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Canadian Environmental Protection Act

PRIORITY SUBSTANCES LIST

ASSESSMENT REPORT

ETHYLENE OXIDE

Environment Canada
Health Canada

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LIST OF ACRONYMS AND ABBREVIATIONS

ARET	Accelerated Reduction/Elimination of Toxics
BMC	Benchmark Concentration
BOD	biological oxygen demand
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CFC	chlorofluorocarbon
CI	confidence interval
CL	confidence limit
CTV	Critical Toxicity Value
EEV	Estimated Exposure Value
ENEV	Estimated No-Effects Value
EPI	Exposure Potency Index
GSTT1	theta-class glutathione S-transferase
GWP	Global Warming Potential
7-HeGua	7-(2-hydroxyethyl)guanine
HEHis	hydroxyethylhistidine
HEVal	N-(2-hydroxyethyl)valine
Hprt	hypoxanthine phosphoribosyl transferase
IC$_{50}$	median inhibitory concentration
K$_{oc}$	sorption partition coefficient
K$_{ow}$	octanol/water partition coefficient
kg-bw	kilogram body weight
LC$_{50}$	median lethal concentration
LCL	lower confidence limit
LD$_{50}$	median lethal dose
NPRI	National Pollutant Release Inventory
ODP	Ozone Depletion Potential
OR	odds ratio
PBPK	physiologically based pharmacokinetic
POCP	Photochemical Ozone Creation Potential
PSL	Priority Substances List
RR	relative risk
SD	standard deviation
SE	standard error
SIR	standardized incidence ratio
SMR	standardized mortality ratio
mSMR	meta standardized mortality ratio
sSMR	summary standardized mortality ratio
TC$_{05}$	Tumorigenic Concentration$_{05}$; concentration causing a 5% increase in tumour incidence over background
ThOD	theoretical oxygen demand
TWA	time-weighted average

Synopsis

Ethylene oxide (CAS No. 75-21-8) is a colourless, highly reactive gas at room temperature and pressure. It has a high vapour pressure and high water solubility.

Domestic production of ethylene oxide in 1996 was 625 kilotonnes, 95% of which was used in the manufacture of ethylene glycol. An estimated 4% was used in the manufacture of surfactants. Ethylene oxide is also used as a sterilant for health care materials and other heat-sensitive products. Releases of ethylene oxide from natural sources, such as waterlogged soil, are expected to be negligible. Anthropogenic sources, not including sterilization, released an estimated 22.8 tonnes, all to the atmosphere, in 1996, down from 104 tonnes in 1993. An estimated 3 tonnes per year were lost to the atmosphere in 1996 from servicing medical facilities using ethylene oxide in sterilization processes and commercial sterilization operations.

Based on empirical fate data, release of ethylene oxide to the atmosphere is unlikely to result in transfer to other environmental compartments in significant quantities. Atmospheric half-lives are based on reaction with photogenerated hydroxyl radicals and range from 38 to 382 days. In the event of release or spill to water, ethylene oxide is expected to be susceptible to evaporation, hydrolysis, and aerobic and, to a lesser extent, anaerobic biodegradation. In water, experimental results show the volatilization half-life to be 1 hour, the hydrolysis half-life to be 12–14 days, the aerobic biodegradation half-life to be from 20 days to 6 months and the anaerobic biodegradation half-life to be from 4 months to 2 years. In soil, ethylene oxide is expected to volatilize rapidly. The hydrolysis half-lives for soil and groundwater are estimated to be between 10.5 and 11.9 days.

Data on toxicity for organisms in the aquatic and terrestrial environments are limited. Most ethylene oxide is released to the atmosphere, and little transfer to water or soil is expected. Therefore, the potential for adverse effects is greatest for terrestrial organisms exposed to contaminated air. There were no available studies examining the effects on wild mammal and bird species; consequently, chronic effects observed in laboratory animals were assumed to reflect those in wild species. From these studies, the most significant endpoint with the greatest potential to result in population-level effects in wildlife was the induction of adverse reproductive effects in rats following inhalation at 183 mg/m^3. This study was chosen as the most critical to the assessment and was used as a basis for the generation of an Estimated No-Effects Value (ENEV). Comparison of the worst-case average concentration in air (956 μg/m^3) with the ENEV (1830 μg/m^3) indicates that it is unlikely that terrestrial organisms are exposed to harmful levels of ethylene oxide in the Canadian environment.

Ethylene oxide is not expected to contribute to the formation of ground-level ozone or to the depletion of the stratospheric ozone layer. Its contribution as a greenhouse gas is also considered to be negligible.

The focus of the human health assessment is airborne exposure. Based on studies in animals, cancer is considered the critical endpoint for effects of ethylene oxide on human health. In inhalation studies, ethylene oxide has induced a wide range of tumours, with a strong likelihood that the mode of action involves direct interaction with genetic material. As a result, there is considered to be a probability of harm at any level of exposure. While there is some evidence of an association between exposure to ethylene oxide and the development of hematological cancers in epidemiological studies of occupationally exposed populations, limitations of the data preclude definitive conclusions.

Based on the information available, it is proposed that ethylene oxide is not entering the environment in a quantity or concentration or under conditions having or that may have an immediate or long-term harmful effect on the environment or constituting or that may constitute a danger to the environment on which human life depends. Ethylene oxide is considered to be entering the environment in a quantity or concentration or under conditions constituting or that may constitute a danger in Canada to human life or health and therefore is proposed to be "toxic" under Section 11 of the *Canadian Environmental Protection Act* (CEPA).

Based on comparison of extremely limited monitoring data and primarily predicted concentrations of ethylene oxide in air with tumorigenic potency, it is recommended that options to reduce exposure, particularly in the vicinity of point sources, be investigated. It is also recommended that there be additional investigation of the magnitude of exposure of populations in the vicinity of point sources as a basis for risk management.

1.0 INTRODUCTION

The *Canadian Environmental Protection Act* (CEPA) requires the federal Ministers of the Environment and of Health to prepare and publish a Priority Substances List (PSL) that identifies substances, including chemicals, groups of chemicals, effluents and wastes, that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" as defined in Section 11 of the Act, which states:

> ...a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions
> (a) having or that may have an immediate or long-term harmful effect on the environment;
> (b) constituting or that may constitute a danger to the environment on which human life depends; or
> (c) constituting or that may constitute a danger in Canada to human life or health.

Substances that are assessed as "toxic" as defined in Section 11 may be placed on Schedule I of the Act and considered for possible risk management measures, such as regulations, guidelines or codes of practice to control any aspect of their life cycle, from the research and development stage through manufacture, use, storage, transport and ultimate disposal.

Based on initial screening of readily accessible information, the rationale for assessing ethylene oxide provided by the Ministers' Expert Advisory Panel on the Second Priority Substances List (Ministers' Expert Advisory Panel, 1995) was as follows:

> Large volumes of ethylene oxide are used to produce ethylene glycol. Ethylene oxide is present in fossil fuel emissions and tobacco smoke. It is released in gaseous and liquid forms during its production, and from its use in manufacturing other compounds. Ethylene oxide is a human carcinogen and is mutagenic to animals. It was determined that an assessment is necessary to characterize the extent of exposure and the associated risk to human health and the Canadian environment.

Descriptions of the approaches to assessment of the effects of Priority Substances on the environment and human health are available in published companion documents. The document entitled "Environmental Assessments of Priority Substances under the *Canadian Environmental Protection Act*. Guidance Manual Version 1.0 — March 1997" (Environment Canada, 1997a) provides guidance for conducting environmental assessments of Priority Substances in Canada. This document may be purchased from:

Environmental Protection Publications
Environmental Technology Advancement Directorate
Environment Canada
Ottawa, Ontario
KIA 0H3

It is also available on the Internet at www.ec.gc.ca/cceb1/eng/psap.htm under the heading "Technical Guidance Manual."

The approach to assessment of effects on human health is outlined in the following publication of the Environmental Health Directorate of Health Canada: "*Canadian Environmental Protection Act* — Human Health Risk Assessment for Priority Substances" (Health Canada, 1994), copies of which are available from:

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

or on the Environmental Health Directorate publications web site (www.hc-sc.gc.ca/ehp/ehd/catalogue/bch.htm). The approach is also described in an article published in the *Journal of Environmental Science and Health — Environmental Carcinogenesis & Ecotoxicology Reviews* (Meek *et al.*, 1994). It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which are described on the Environmental Substances Division web site (www.hc-sc.gc.ca/ehp/ehd/bch/env_contaminants/psap/psap.htm) and which will be addressed in future releases of the approach paper for the assessment of effects on human health.

The search strategies employed in the identification of other data relevant to assessment of potential effects on the environment (prior to May 1998) and human health (prior to January 1999) are presented in Appendix A. Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether ethylene oxide is "toxic" under CEPA have been critically evaluated by staff of Environment Canada (entry and environmental exposure and effects) and Health Canada (human exposure and effects on human health).

Sections of this Assessment Report and supporting documentation (Environment Canada, 1999) related to the environmental assessment of ethylene oxide were prepared by M. Lewis of Environment Canada. An initial draft of the environmental assessment was prepared by D. Moore and S. Teed of Cadmus Group Inc. on behalf of Environment Canada. Other members of the Environmental Resource Group who reviewed the documents and participated in discussions were:

M. Alaee, Environment Canada
Y. Bovet, Environment Canada
N. Bunce, University of Guelph
L. Hamel, Union Carbide Canada Inc.
R. Kent, Environment Canada
G. Parsons, Huntsman Corp.
J. Prinsen, Environment Canada
R. Romano, Chemical Manufacturers Association
S. Smythe-Plewes, Ontario Hospital Association

The environmental sections of the Assessment Report and supporting documentation (Environment Canada, 1999) were also reviewed by internal reviewers at Environment Canada — namely, K. Lloyd and P. Doyle — as well as by external reviewers: D. Maletski (BUA, Germany) and D. Markwordt (U.S. Environmental Protection Agency).

The health-related sections of this Assessment Report and supporting documentation were prepared by the following staff of Health Canada:

R. Beauchamp
W. Bruce
R.G. Liteplo
M.E. Meek
D. Moir
M. Walker

Sections of the supporting documentation and Assessment Report on genotoxicity were reviewed by G. Douglas (Environmental and Occupational Toxicology Division, Health Canada). In order to address primarily adequacy of coverage, sections of the supporting documentation pertaining to human health were reviewed externally by:

T. Fennel, Chemical Industry Institute of Toxicology
R. Gingell, Shell Chemical Co.
L. Recio, Chemical Industry Institute of Toxicology
W.M. Snellings, Union Carbide
M.J. Teta, Union Carbide
V. Walker, New York State Department of Health

Accuracy of reporting, adequacy of coverage and defensibility of conclusions with respect to hazard characterization and dose–response analysis were considered in written review by staff of the Information Department of BIBRA International and at a panel meeting of the following members, convened by Toxicology Excellence for Risk Assessment (TERA) on August 12, 1999, in Ottawa, Canada:

M. Bogdanffy, DuPont Haskel Laboratory
J. Christopher, California Environmental Protection Agency
M. Dourson, TERA
S. Felter, Procter & Gamble
J. Mandel, Exponent
R. Rudel, Silent Spring Institute
V. Walker, New York State Department of Health

J. Preston (U.S. Environmental Protection Agency) provided written comments on the draft supporting documentation, hazard characterization and dose–response analysis.

The health-related sections of the Assessment Report were reviewed and approved by the Health Protection Branch Risk Management meeting of Health Canada.

The entire Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

The text of the Assessment Report has been structured to address environmental effects initially (relevant to determination of "toxic" under Paragraphs 11(a) and (b)), followed by effects on human health (relevant to determination of "toxic" under Paragraph 11(c)).

Copies of this Assessment Report are available upon request from:

Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or on the Internet at:

www.ec.gc.ca/cceb1/eng/public/index_e.html

Unpublished supporting documentation, which presents additional information, is available upon request from:

Commercial Chemicals Evaluation Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or

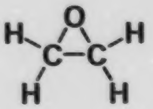
Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

2.0 SUMMARY OF INFORMATION CRITICAL TO ASSESSMENT OF "TOXIC" UNDER CEPA

2.1 Identity and physical/chemical properties

Ethylene oxide is also known as diethylene oxide, E.O., epoxyethane, 1,2-epoxyethane, oxane, oxidoethane and oxirane. Its Chemical Abstracts Service (CAS) registry number is 75-21-8. The chemical structure of ethylene oxide is shown in Figure 1.

Figure 1: Chemical structure of ethylene oxide



The molecular formula for ethylene oxide is H_2COCH_2, and its molecular weight is 44.05. At room temperature (25°C) and normal atmospheric pressure, ethylene oxide is a colourless, highly reactive and flammable gas with a characteristic ethereal odour. It has a high vapour pressure (~146 kPa) and high water solubility (completely miscible). It is very reactive in both the liquid and vapour phases (WHO, 1985). Table 1 summarizes the physical and chemical properties of ethylene oxide.

The conversion factor for airborne ethylene oxide used throughout this report is 1 ppm = 1.83 mg/m^3.

2.2 Entry characterization

2.2.1 Production, uses and importation

Canadian companies that currently produce ethylene oxide include Dow Chemical Canada Ltd., Union Carbide Canada Inc. and Alberta & Orient Glycol. Domestic production was estimated at 625 kilotonnes in 1996, and the forecasted total estimated for 1999 was 682 kilotonnes (CPI, 1997). Dow Chemical Canada Ltd., in Alberta, had an estimated 60-kilotonne increase in production capacity between 1981 and 1992 and a forecasted 50-kilotonne increase between 1996 and 1999 (CPI, 1997). Alberta & Orient Glycol went into operation in September 1994 and has a potential capacity of 215 kilotonnes per year. Canadian import volumes for 1992, 1994 and 1996 were 4.39, 10.97 and 8.00 kilotonnes, respectively (CPI, 1997). Totals of 36 and 18 kilotonnes were exported in 1992 and 1996, respectively (CPI, 1997).

Shell Chemicals Canada intends to build a world-scale ethylene oxide/glycol plant at Scotford, Alberta, to help meet the growing worldwide demand for glycol. All of the ethylene oxide produced will be used in the synthesis of ethylene glycol, with an expected capacity of 400 kilotonnes per year. The new Scotford plant will supply customers in North America and the Far East starting in the year 2000 (CPI, 1997).

Virtually all of the ethylene oxide produced is used as an intermediate in the production of various chemicals (ATSDR, 1990). In 1993, 89% of the total Canadian production of ethylene oxide was used in the production of ethylene glycol (SRI, 1993); in 1996, 95% was used for this purpose (CPI, 1997). It is forecasted that the volume used in ethylene glycol production will continue to increase. An estimated 4% (26 000 tonnes) is used in the manufacture of surfactants (CPI, 1997). Ethylene oxide alone or in combination with other inert gases such as carbon dioxide and nitrogen is used to sterilize instruments from the health care, publication and wood products sectors. Ethylene oxide is also used in other industries where heat-sensitive goods are sterilized (How-Grant, 1991; BUA, 1995). In Canada, ethylene oxide is also used in the manufacture of choline chloride, glycol ethers and polyglycols (CPI, 1997). Other minor uses worldwide include use in the manufacture of rocket propellant and petroleum demulsifiers (Lewis, 1993).

Alternatives to ethylene oxide use in sterilization are available and include hydrogen peroxide, gas plasma, peracetic acid, ozone, chlorine dioxide, and low-temperature steam and formaldehyde. Some of the main advantages of using ethylene oxide as a sterilant are that it is very effective at penetrating most wrappings of paper and cloth, does not damage the materials or packaging and requires relatively low temperatures and pressures (BUA, 1995).

Ethylene oxide is used as an active ingredient in one registered pest control product in Canada for the control of insects in stored products and the control of bacteria in spices and natural seasonings. The quantity of ethylene oxide used as a fumigant in Canada is unknown (Ballantine, 1997). Ethylene oxide is also found as a formulant or component of a formulant in 25 other pest control products. In all 25 cases, amounts of ethylene oxide range from trace to 0.423%. The formulants include fungicides, insecticides, herbicides and an adjuvant (Ballantine, 1997). The use of ethylene oxide as an active ingredient in agricultural pesticides is not considered further in this assessment, as such use is regulated under the *Pest Control Products Act*.

2.2.2 Sources and releases

2.2.2.1 Natural sources

Ethylene oxide is known to be produced from a few natural sources. In certain plants, ethylene (a natural plant growth regulator) is degraded to ethylene oxide (Abeles and Dunn, 1985). It is also a product of ethylene catabolism in certain microorganisms (De Bont and Albers, 1976). Ethylene oxide can be generated from waterlogged soil (Smith and Jackson, 1974; Jackson *et al.*, 1978), manure and sewage sludge (Wong *et al.*, 1983). Quantitative estimates of production from these natural sources are not available, but emissions are expected to be negligible.

2.2.2.2 Anthropogenic sources

2.2.2.2.1 Non-point sources

There are several non-point sources of release of ethylene oxide. Safety precautions taken when handling and transporting the chemical, because of its explosive nature, seem to have reduced the incidence of spills. From the National Analysis of Trends in Emergency Systems database, only one spill was reported, and that was the release, due to human error, of 0.127 kg of ethylene oxide to soil at a government facility in Halifax, Nova Scotia (NATES, 1994). The CANUTEC database (Transport Canada, 1996) reported several incidents involving the release of ethylene oxide from derailed train tanker cars and truck accidents. Concentrations in the environment from these releases were not reported.

Other recognized non-point sources of release of ethylene oxide include its formation from fossil fuel combustion (U.S. EPA, 1984) and presence in tobacco smoke (Howard, 1989). Neither source is expected to be significant (U.S. EPA, 1984). Ethylene oxide is used as a component in the production of polyoxyethylene surfactants at high molar concentrations (5–20 mol/L) (Gaskin and Holloway, 1992). These surfactants increase the effectiveness of herbicide applications to plants; however, the ethylene oxide in this form is bound within the surfactant molecule, and any release is expected to be minimal. Similarly, ethylene oxide may be present in nonylphenol ethoxylate formulations at concentrations below 10 mg/L (Talmage, 1994), and, according to German manufacturers, ethylene oxide may remain as a contaminant at 0.001% or 10 mg/kg in liquid detergents from the production of non-ionic surfactants (BUA, 1995). Examination of the Material Safety Data Sheets for more than 15 different ethylene oxide-derived surfactants revealed final product concentrations at trace amounts (i.e., <1 ppm). A variety of other products, including paints and coatings, were reported to contain ethylene oxide at levels ranging from trace to <0.5%. The diffuse release of such quantities is expected to result in negligible environmental concentrations.

Ethylene oxide is used for the control of insect (i.e., fumigation) and microbial (i.e., sterilization) infestations. Estimates of the concentrations of ethylene oxide required for these purposes range from 250 to 1500 mg/L (Agriculture and Agri-Food Canada, 1996; Conviser, 1999; Health Canada, 1999a). Residues of ethylene oxide following the fumigation or sterilization of foods include unreacted ethylene oxide and various degradation products. Following fumigation, any residual ethylene oxide in foodstuffs disappears rapidly; concentrations generally fall to negligible levels within a few hours (IARC, 1976). However, degradation products of ethylene oxide (e.g., ethylene chlorohydrin) are generally less volatile and more persistent within foodstuffs. The presence and concentrations of such residues after fumigation or sterilization depend upon the concentration of ethylene oxide, temperature, aeration, storage conditions after treatment, the type of commodity, its moisture and lipid content and other factors (WHO, 1985). In Canada, ethylene oxide is permitted to be used (*Food and Drug Act*, 1996) only as a food additive (fumigant) on "whole or ground spices except mixtures containing salt" at levels consistent with "good manufacturing practice" (i.e., the minimum amount required to achieve the intended effect). A legal tolerance of 1500 mg/kg has been established for spices (Health Canada, 1999a) with respect to the content of ethylene chlorohydrin, formed by the reaction of ethylene oxide with inorganic chlorides contained in the food. A proposal to establish a tolerance limiting residues of ethylene oxide used as a food additive in spices to 50 mg/kg is under consideration (Le Maguer, 1999).

2.2.2.2.2 Point sources

Gas and liquid forms of ethylene oxide can be released during production and use, as well as during the manufacture of ethylene glycol, ethoxylates, ethers and ethanolamines (Howard, 1989). Ethylene oxide releases to the Canadian environment as reported to the National Pollutant Release Inventory (NPRI) totalled 103.9 tonnes in 1993, 51.1 tonnes in 1994, 26.2 tonnes in 1995 and 22.8 tonnes in 1996 (NPRI, 1993, 1994, 1995, 1996). Between 1994 and 1995, there was an overall reduction of 49%, with the decline in releases attributable to Huntsman Corp. (decreased 88%), Dow Chemical Canada Inc. (decreased 66%) and Union Carbide Canada Inc. (decreased 41%). Twelve facilities were identified in 1994, 11 in 1995 and 10 in 1996, with all releases being to the atmospheric environment. Alberta and Ontario contributed 41% and 35% of the total releases, respectively, in 1995 (NPRI, 1995). The industrial sectors reporting releases of ethylene oxide include plastics and synthetics, inorganic chemicals (6.1 tonnes per year), industrial organic chemicals (8.7 tonnes per year) and soap and cleaning compounds (8.0 tonnes per year), with the quantities from the latter sector expected to diminish by 5.3 tonnes in 1997 (NPRI, 1996). An Environment Canada survey of Canadian industry regarding ethylene oxide use and release, which was carried out under the authority of Section 16 of CEPA, revealed three additional facilities releasing a total of 3.5 tonnes in 1996. Two of these companies are involved in servicing medical facilities using ethylene oxide in sterilization processes and commercial sterilization operations and account for 86% (3.0 tonnes) of the release volume from this sector (Environment Canada, 1997b).

The Accelerated Reduction/Elimination of Toxics (ARET) program has reported emissions of 19 tonnes for 1997 by participating companies, with emissions reduced by 82% from the 1993 levels. Eight of the 10 facilities reporting to NPRI in 1996 are participating in ARET (ARET, 1999).

Ethylene oxide emissions from specific chemical production processes were estimated at 389 tonnes per year from an ethylene oxidation processing plant producing 210 000 tonnes per year under no control measures and reduced to 21.5 tonnes per year with the appropriate controls (Shen and Minns, 1997). Similarly, estimated emissions from an ethylene glycol manufacturing plant were 7.2 tonnes per year with no control devices and 0.36 tonnes per year with control devices (Shen and Minns, 1997). These estimates were slightly higher than releases reported from Dow Chemical Canada Inc. and Union Carbide Canada Inc., the two major ethylene oxide production facilities in Canada, which reported releases of 6.1 and 4.6 tonnes, respectively, in 1996 (NPRI, 1996).

An examination of the fugitive emissions from U.S. ethylene oxide production facilities in 1988 suggests that significant emissions can occur as a result of faulty design and inadequate maintenance or monitoring (Berglund *et al.*, 1990). Data were collected from most of the ethylene oxide producers within the United States as part of a cooperative agreement between the Ethylene Oxide Industry Council, a trade association within the Chemical Manufacturers Association, and the U.S. Environmental Protection Agency (EPA). This study found that, overall, 86.9% of the components (i.e., gas valves, liquid valves, safety valves, pumps, flanges, open-ended lines, compressors) did not leak (<10 mg/m^3), 10.3% were low emitters (100–1000 mg/m^3), 0.6% were high emitters (>1000 mg/m^3) and 0.6% were leakers (>10 000 mg/m^3). Over 90% of the safety valves had no measurable level; however, leaking pumps and flanges accounted for 30 and 40% of the total estimated ethylene oxide emissions, respectively (Berglund *et al.*, 1990).

Although sterilization is not a major use of ethylene oxide in terms of volumes consumed, it may be a very significant source of release to the environment (WHO, 1985). A survey of hospitals using ethylene oxide as a sterilizing agent was conducted in April 1994 by the Canadian Hospital Association (CHA and Environment Canada, 1994). Of the 204 hospitals contacted in all provinces and territories, 89 (44%) responded. A total of 70 (79%) of the respondents used ethylene oxide in a proportion of 12%, and the remaining 19 (21%) used it at 100%. In Canada, the amount of ethylene oxide used as a sterilant can be only roughly estimated. Based on the 1994 estimate of the volume of chlorofluorocarbon (CFC) used in sterilization facilities of 231 tonnes (Madé, 1996) and assuming that 79% of Canadian hospitals use the common ratio of ethylene oxide to carrier gas of 12:88 during sterilization operations (Meiners and Nicholson, 1988; CHA and Environment Canada, 1994), an estimated 31.5 tonnes of ethylene oxide were used in 1994 for sterilization at these facilities. Assuming that the remaining 21% of hospitals use it at 100% strength and that the amount of ethylene oxide per sterilization is equivalent to that used in the 12:88 method, an additional 8.4 tonnes are used, for a total of 39.9 tonnes per year. In the past, many hospitals did not have control equipment to reduce emissions; however, many facilities now have improved control measures in place (Havlicek *et al.*, 1992; CHA and Environment Canada, 1994). In addition, owing to the adverse environmental impact of CFCs, many hospitals have begun to use alternative equipment that does not involve use of ethylene oxide (Smyth-Plewes, 1998). The current volumes of ethylene oxide used and released may be significantly less than the 1994 estimates.

The environmental control measures on sterilization equipment vary from virtually 100% control (CHA and Environment Canada, 1994) to no control (Markwordt, 1985). In the United States, more than 50% of the medical devices manufactured are sterilized with ethylene oxide, and every hospital performing surgery has at least one ethylene oxide sterilizer (How-Grant, 1991).

In an examination of the primary U.S. sources of ethylene oxide releases, sterilization/fumigation sites, production/captive use, medical facilities and ethoxylation account for 57, 31, 8 and 4% of total emissions, respectively (Markwordt, 1985). In an early U.S. study, it was estimated that <0.1% of ethylene oxide produced is used as a sterilizing agent or fumigant, yet this accounts for the majority of ethylene oxide released into the atmosphere (Markwordt, 1985). Similarly, Berkopec and Vidic (1996) found that, in Slovenia, emissions to the atmosphere during sterilization were higher than emissions from other processes, such as synthesis of glycols and other derivatives in the chemical industry, although the sterilization process accounts for only 2% of total ethylene oxide use. In Belgium, an estimated 0.07% of the total consumption of ethylene oxide was used in sterilization operations in health care and medical products industries (Wolfs *et al.*, 1983).

The type of equipment and operation of sterilization facilities can influence the quantity of ethylene oxide released. Essentially, all facilities that control sterilizer vent emissions (usually greater than 99% removal efficiency) have recirculating-water vacuum pumps, which result in no loss of ethylene oxide through the water drain (Meiners and Nicholson, 1988; U.S. EPA, 1992, 1994). The Standards Council of Canada recommends that a liquid/gas separator be installed so that the liquid effluent is directed to the sanitary floor drain and the gas effluent is discharged through the local exhaust ventilation (CSA, 1991). In those facilities that use once-through water-sealed vacuum pumps, some ethylene oxide dissolved in the water will be directed to a floor drain and will likely volatilize to the atmosphere at an outdoor ground-level drain near the facility or wastewater treatment facility (U.S. EPA, 1992; WCB, 1994). Hospital sterilizer discharge experiments conducted in the United States on catalytic oxidation systems revealed absorption of ethylene oxide between 22 and 78% in the wastewater (Leclair *et al.*, 1988; Meiners and Nicholson, 1988). Examination of the vacuum pump water discharge revealed rapid and complete loss of the ethylene oxide within 7 minutes from an initial concentration of 15 000 mg/L (Meiners and Nicholson, 1988).

In summary, the available data from point sources of release of ethylene oxide indicate that essentially all releases are to the atmosphere and that there has been a notable reduction in emissions in Canada, as evidenced by release trends reported through NPRI, progress through the ARET program and available information on releases from sterilization facilities. It is not clear how the new Shell Chemicals plant in Scotford, Alberta, will impact on the release trend; however, the predicted increase in production volume could slow this decline.

2.3 Exposure characterization

2.3.1 Environmental fate

Based on empirical fate data, release of ethylene oxide to the atmosphere is unlikely to result in transfer to other environmental compartments in significant quantities. Reaction half-life in the atmosphere may be significantly long ($t_{½}$ between 38 and 382 days); however, evidence also indicates that washout by precipitation can be important where subsequent hydrolysis can occur ($t_{½}$ between 9 and 14 days). Revolatilization from the water is also expected to be rapid ($t_{½}$ ~1 hour). On the basis of a low log K_{ow} (–0.30), the potential for bioaccumulation of ethylene oxide is expected to be very low. As a result of its high water solubility and vapour pressure, ethylene oxide is not expected to bioaccumulate or accumulate in sediment or soil.

2.3.1.1 Air

The atmospheric half-lives for ethylene oxide following vapour-phase reactions with photochemically produced hydroxyl radicals, assuming an atmospheric concentration of hydroxyl radicals of 1×10^6 radicals/cm^3, were estimated at 120 days (Atkinson, 1986), 99 days (Lorenz and Zellner, 1984), 151 days (Zetzsch, 1985) and between 38 and 382 days (Howard *et al.*, 1991).

If one considers that the hydroxyl radical concentration changes as a function of light duration and intensity, then the half-life can vary with latitude across Canada. By similar calculation, using an estimated hydroxyl radical concentration for Montreal, Quebec, around the March equinox of 8.6×10^5 radicals/cm^3 (Bunce, 1997) and the experimental rate constant of 0.053×10^{-12} cm^3/molecule per second (Zetsch, 1985), a half-life of 176 days is estimated for that location.

The theoretical atmospheric lifetimes (approximately $1.43 \times t_{½}$) for ethylene oxide were estimated at ~200 days (Bunce, 1996) and 330 days (Winer *et al.*, 1987) and were calculated based on the reaction with hydroxyl radicals at a concentration of 8.0×10^5 and 1.0×10^6 radicals/cm^3, respectively. Such lifetimes are expected to be long enough to allow a very small percentage of the amount emitted to reach the stratosphere (Bunce, 1996).

Ethylene oxide has a very high water solubility (completely miscible), which would suggest that some washout via precipitation can be expected; however, its high vapour pressure (~146 kPa) and rapid volatilization rate may limit the effectiveness of this process. An examination of the effect of atmospheric precipitation was conducted in a laboratory setting (Winer *et al.*, 1987), resulting in evidence that washout has little impact on reducing atmospheric concentrations.

2.3.1.2 Water

Ethylene oxide is expected to undergo numerous fate processes in water, including evaporation, hydrolysis, and aerobic and anaerobic biodegradation. Evaporation from water appears to be a significant removal process. The reported experimental aquatic half-life for evaporation of ethylene oxide in water is 1 hour with no wind and 0.8 hours with a 5 m/s wind (Conway *et al.*, 1983). Ethylene oxide degrades in water by hydrolysis and other nucleophilic reactions (U.S. EPA, 1985). Ethylene oxide is hydrolyzed in fresh water to ethylene glycol and in salt water to ethylene glycol and ethylene chlorohydrin. The half-life was estimated experimentally to be 12–14 days for hydrolysis at pH 5–7 in fresh water and 9–11 days in salt water (Conway *et al.*, 1983). The aqueous aerobic biodegradation half-life of ethylene oxide was approximately 20 days from a lightly seeded biological oxygen demand (BOD) test, and the rate in a biological waste treatment system is expected to be much faster (Conway *et al.*, 1983). Based on the BOD test results of Bridié *et al.* (1979a) and Conway *et al.* (1983), Howard *et al.* (1991) estimated the unacclimated aqueous biodegradation half-life to be from 1 to 6 months. The aqueous anaerobic half-life, based on the estimated aerobic biodegradation half-life, is 4–24 months (Howard *et al.*, 1991). The 5-day BOD was 3% of the theoretical oxygen demand (ThOD) of 1.82 g/g (Bridié *et al.*, 1979a).

2.3.1.3 Soil and sediment

Ethylene oxide is miscible in water and poorly adsorbed to soil, so it has the potential to leach into groundwater (HSDB, 1999). Because of its high vapour pressure (146 kPa), a spill of ethylene oxide to soil will result in most volatilizing to the atmosphere, with only a small fraction infiltrating the soil. Evaporation will continue within the soil, but at a reduced rate (Environment

Canada, 1985). Dilution with water will reduce the velocity at which the ethylene oxide moves downward and at the same time diminish the vapour pressure and reduce the rate of evaporation. Upon reaching the groundwater table, ethylene oxide will move in the direction of groundwater flow. The half-lives for hydrolysis in groundwater and soil are estimated to be between 10.5 and 11.9 days, based on measured rate constants at pH 5, 7 and 9 (Mabey and Mill, 1978; Howard *et al.*, 1991). In general, volatilization is the primary removal mechanism, but ethylene oxide is expected to hydrolyze and be biodegraded relatively rapidly in most soils.

There is no information available on the environmental fate of ethylene oxide in sediment. Because of its physical and chemical properties, ethylene oxide is not expected to be sorbed by sediment or soil.

2.3.1.4 Biota

There are no reported levels of ethylene oxide in environmental biota. Ethylene oxide has a high vapour pressure (146 kPa) and high water solubility (infinitely soluble) (Table 1). On the basis of a low log K_{ow} (–0.30), the potential for bioaccumulation of ethylene oxide is expected to be very low (Verschueren, 1983; Howard, 1989).

2.3.1.5 Environmental partitioning

Fugacity modelling was conducted to characterize key reaction, intercompartment and advection (movement out of a system) pathways for ethylene oxide and its overall distribution in the environment. A steady-state, non-equilibrium model (Level III fugacity model) was run using the methods developed by Mackay (1991) and Mackay and Paterson (1991). All physical and chemical property input values were selected from a compilation of literature values based on criteria for integrity (see DMER and AEL, 1996, for details). The key parameters are shown in Table 2.

Based on the ChemCAN Level III fugacity model, which depicts a mixedwood plain region of a densely populated region of southern Ontario, it is estimated that ethylene oxide will have an overall persistence of 3 days in that region from a reaction persistence estimated at 70 days. Owing to its short overall persistence, higher concentrations will likely be centralized in areas close to discharges. Based on the 1993 NPRI release volume of 53 200 kg to the atmosphere in southern Ontario (NPRI, 1993), the average steady-state levels in the southern Ontario region are estimated at 1.02 ng/m^3 in air (344 kg), 0.067 ng/L in water (99.0 kg), 6.03×10^{-5} ng/g in soil (0.858 kg) and 3.27×10^{-5} ng/g in sediment (0.034 kg). Bioaccumulation is not expected (DMER and AEL, 1996).

The concentrations of ethylene oxide predicted above are based on the assumption that air entering southern Ontario from neighbouring regions contains no ethylene oxide. Estimates of concentrations of ethylene oxide in air in the 48 contiguous states of the United States, derived from atmospheric dispersion modelling and U.S. emission inventories, are available from the U.S. EPA's Cumulative Exposure Project (Woodruff *et al.*, 1998). Mean concentrations predicted for 1990 in Michigan and New York, which border southern Ontario, were 4.9 ng/m^3

and 5.9 ng/m^3, respectively. When the average of these concentrations was assumed for the concentration of ethylene oxide in air advected into southern Ontario, the concentrations predicted by the ChemCAN model increased approximately 6-fold, to 6.2 ng/m^3 in air, 0.4 ng/L in water, 3.7×10^{-4} ng/g in soil and 2.0×10^{-4} ng/g in sediment. Concentrations predicted in the ChemCAN auxiliary compartments of terrestrial animals and terrestrial plants were 4.3×10^{-5} ng/g and 1.4×10^{-3} ng/g, respectively, when this additional advective input was included in the fugacity modelling (Health Canada, 1999a).

2.3.2 Environmental concentrations

2.3.2.1 Ambient air

Data on concentrations of ethylene oxide in ambient air in Canada are very limited. Information on levels in emissions from Canadian production, processing or sterilization facilities was not identified.

Ethylene oxide was detected at concentrations of 3.7, 3.9 and 4.9 µg/m^3 in 3 of 50 24-hour samples of air collected outside of randomly selected residences during a multimedia exposure study conducted in Canada (Health Canada, 1999a). The censored mean value was 0.34 µg/m^3 when a concentration equivalent to one-half the limit of detection (i.e., ½ × 0.19 µg/m^3 = 0.095 µg/m^3) was assumed for the 47 samples in which ethylene oxide was not detected. Ethylene oxide was detected at 3 (or 33%) of 9 locations in Alberta, but at none of the 35 locations in Ontario or the 6 locations in Nova Scotia during this study (Health Canada, 1999a).

Based on data on 1993 air quality modelling predictions from a Canadian production facility, obtained from a survey of Canadian industry carried out under the authority of Section 16 of CEPA (Environment Canada, 1997b), it was estimated that 1-hour average ground-level concentrations of ethylene oxide would exceed 12 µg/m^3 a total of 17 hours a year in the immediate vicinity of the plant. Predicted maximum 1-hour-average ground-level concentrations ranged from 3.7 to 20.1 µg/m^3 at distances of 5 and 2.7 km from the plant, respectively. No measurements were available to validate these predictions.

Estimated maximum average daily concentrations of ethylene oxide in the vicinity of Canadian hospitals were 0.26, 0.83, 1.3 and 2.12 µg/m^3 between 100 and 70 m from the emission source and from stack heights of 30, 18, 15 and 12 m, respectively. Concentrations closer to or farther from the source are predicted to be less. The estimate was based on the U.S. EPA "SCREEN3" Gaussian plume model, which incorporates source-related and meteorological factors to estimate pollutant concentration from continuous sources. The model assumes that the pollutant does not undergo any chemical reactions and that no other removal processes, such as wet or dry deposition, act on the plume during its transport from the source (U.S. EPA, 1995) (see Table 3 for input parameters).

In an assessment of emissions and concentrations of ethylene oxide throughout California, mean 24-hour ambient air concentrations sampled in Los Angeles ranged from 0.038 to 955.7 µg/m^3 (n = 128) (Havlicek *et al.*, 1992). The authors reported that heavy usage of ethylene oxide within the Los Angeles basin coupled with restricted airflow out of the basin likely led to the large range of ambient air concentrations. There was a high degree of local variability that would be consistent with the release of ethylene oxide during a sterilization cycle. Air concentrations sampled in northern California ranged from 0.032 to 0.40 µg/m^3 (n = 36). At remote coastal locations in California, ethylene oxide concentrations ranged from 0.029 to 0.36 µg/m^3 (n = 22). The authors warn that it is difficult to make any definitive statements regarding the spatial and temporal distribution of ethylene oxide based on the samples collected. Air concentrations were found to be very variable, especially in urban areas, with 100-fold shifts in air concentrations over a few minutes.

In a modelling study on point sources of ethylene oxide from sterilizers, information on characteristics of 17 sources in Duval County, Florida, and their emissions was collected in survey questionnaires in 1989 (Tutt and Tilley, 1993). Peak short-term and long-term ambient concentrations of ethylene oxide as a result of emissions from four sterilization facilities identified were estimated based on the U.S. EPA's SCREEN and Industrial Source Complex Short-Term dispersion models. These included a commercial spice fumigation facility (with estimated annual emissions of ethylene oxide of 1959.5 kg per year) and three hospitals of decreasing emission profiles (i.e., from 210.9 to 2.1 kg per year). The predicted maximum average annual concentrations from the two highest emitters were 11 µg/m^3 and 2 µg/m^3, both at distances 32 m from their respective point sources.

2.3.2.2 Indoor air

Ethylene oxide was detected at a concentration of 4 µg/m^3 in only 1 of 50 24-hour samples of air collected inside randomly selected residences during a multimedia exposure study conducted in Canada (Health Canada, 1999a). The censored mean value was 0.17 µg/m^3 when a concentration equivalent to one-half the limit of detection (i.e., $\frac{1}{2} \times 0.19$ µg/m^3 = 0.095 µg/m^3) was assumed for the 49 samples in which ethylene oxide was not detected. Ethylene oxide was detected at concentrations of 5 µg/m^3 in 3 of 24 personal air samples collected from an occupant of each of the 50 residences (Conor Pacific Environmental, 1998).

2.3.2.3 Drinking water

Data on concentrations of ethylene oxide in drinking water were not identified.

2.3.2.4 Surface water

Data on concentrations of ethylene oxide in surface water in Canada were not identified.

2.3.2.5 Sediment and soil

Data on concentrations of ethylene oxide in sediments and soils in Canada were not identified.

2.3.2.6 Biota

Data on concentrations of ethylene oxide in biota in Canada were not identified.

2.3.2.7 Food

Data on the levels of ethylene oxide in foodstuffs consumed in Canada were not identified. Ethylene oxide was detected in 96 (or 47%) of 204 samples of food products taken from retail stores in Denmark in 1985 (Jensen, 1988). The reported concentrations reflect the total amount of ethylene chlorohydrin and ethylene oxide present at the time of analysis. These concentrations ranged from <0.05 to 1800 mg/kg (or μg/g) in the individual samples without correction for recoveries. Ethylene oxide was detected frequently among 24 samples of spices (Jensen, 1988) at a mean concentration of 84 μg/g and a maximum concentration of 580 μg/g.

Ethylene oxide was detected, but not quantified, in 1 of 2372 samples of eggs and in 1 of 3262 samples of fish collected in the United States in 1975 as part of the Food and Drug Administration Monitoring Program (1970–1976) (Duggan *et al.*, 1983).

2.3.2.8 Consumer products

Ethylene oxide may be present in tobacco as a result of its use as a fumigant and sterilizing agent (ATSDR, 1990). It has been detected in smoke from fumigated and unfumigated tobacco at levels of 0.3 and 0.02 μg/mL, respectively (Binder, 1974).

Ethylene oxide may also be present as a contaminant of skin care products. Current commercial preparations of polyglycol ethers may contain residues of ethylene oxide monomer up to approximately 1 μg/g, according to a European study (Filser *et al.*, 1994). Kreuzer (1992) reported concentrations of ethylene oxide monomer in skin care products ranging from 1.9 to 34 nmol/cm^3 (0.08–1.5 mg/L) and a range of maximum skin penetration of ethylene oxide of 1.0–14% in various product formulations.

2.3.2.9 Medical devices

Ethylene oxide is the most common agent currently used for sterilizing disposable dialysers, blood tubing and heat-sensitive medical items and has almost completely replaced formalin for this purpose (Henne *et al.*, 1984; Babich, 1985). Ethylene oxide may be absorbed by medical equipment during sterilization and may remain there as the unchanged compound or as one of its reaction products (WHO, 1985). In studies conducted outside of Canada, concentrations of residual ethylene oxide in medical devices immediately following their sterilization have ranged up to 1 or 2% (Gillespie *et al.*, 1979; Gilding *et al.*, 1980). These concentrations generally declined rapidly after a few days' aeration, although levels exceeding 100 ppm (183 mg/m^3) were sometimes measured following aeration.

2.4 Effects characterization

2.4.1 Ecotoxicology

Information on the toxicity of ethylene oxide to natural aquatic and terrestrial organisms is limited. A brief summary of effects is presented below, with an emphasis on the most sensitive endpoints. A large number of studies have shown that ethylene oxide can induce dose-dependent genetic mutations in various types of biota, including plants, fungi, insects, mammalian cell cultures and bacteria (U.S. EPA, 1985; WHO, 1985; Dellarco *et al.*, 1990; IARC, 1994; BUA, 1995; see also Section 2.4.3.4). The actual population-level impact to wildlife from mutagenic endpoints is not clear. In general, however, these effects occur at levels of ethylene oxide exposure similar to or slightly lower than those observed to induce other effects. A more extensive description of the environmental effects is provided in Environment Canada (1999).

2.4.1.1 Aquatic organisms

Toxicity of ethylene oxide to bacterial cultures has been examined primarily in terms of mutagenicity (Dellarco *et al.*, 1990). Conway *et al.* (1983) examined direct toxicity by determining the IC_{50} for the effect of ethylene oxide on activated sludge microorganisms in a 16-hour bacterial toxicity test at 22°C. The IC_{50} was in the range of 10–100 mg/L (Conway *et al.*, 1983).

In a modified Ames test, direct increases in revertant bacterial mutations in ***Salmonella typhimurium*** strains TA1535 and TA100 were observed (Pfeiffer and Dunkelberg, 1980). Similarly, a dose–response relationship was observed for mutation induction in ***Escherichia coli*** Sd-4 (Hussain, 1984). There was a linear relationship for induction of guanine alkylation at concentrations between 2.6 and ~1000 mg/L for 1-hour exposures. Bacterial survival remained essentially constant at 100% at all dose levels (Hussain, 1984).

Examination of point mutation studies conducted using various strains of bacteria, including DNA repair-deficient strains, revealed positive dose–response relationships following exposure in liquid suspensions up to 4210 mg/L (Dellarco *et al.*, 1990). From the above studies and others, it is difficult to interpret the effects of ethylene oxide on natural bacterial populations in the laboratory when one considers bacterial strains, reproductive potential, natural variability, DNA repair mechanisms and population resilience.

Ethylene oxide appears to be slightly less toxic to invertebrates than to microorganisms. Conway *et al.* (1983) performed a U.S. EPA standard static acute toxicity test on ***Daphnia magna*** that yielded 24-hour LC_{50} values of 260–300 mg/L and 48-hour LC_{50} values of 137–300 mg/L. In acute toxicity tests on brine shrimp (***Artemia salinia***) under similar conditions, 24-hour LC_{50}s were between 350 and 500 mg/L ($n = 3$), and 48-hour LC_{50} values were between 490 and 1000 mg/L ($n = 3$) (Conway *et al.*, 1983).

Fish are moderately sensitive to ethylene oxide. Bridié *et al.* (1979b) examined the acute toxicity of ethylene oxide to goldfish (***Carassius auratus***) and reported a 24-hour LC_{50} of 90 mg/L at 20°C. In acute static toxicity tests performed according to U.S. EPA standards using fathead minnows (*Pimephales promelas*) under aerated conditions, under sealed oxygen or under no aeration, 24-hour LC_{50}s were 274, 86 and 90 mg/L, respectively. With no aeration, the 48- and 96-hour LC_{50}s were 89 and 84 mg/L, respectively (Conway *et al.*, 1983).

2.4.1.1.1 Toxicity of breakdown products

Ethylene glycol and ethylene chlorohydrin are the principal breakdown products of ethylene oxide in water. In acute toxicity tests with ethylene glycol, 24-hour LC_{50}s were >10 000, >10 000 and >20 000 mg/L for the fathead minnow, *Daphnia magna* and brine shrimp, respectively; for ethylene chlorohydrin, 24-hour LC_{50}s were 768, 675 and >1000 mg/L for the fathead minnow, *D. magna* and brine shrimp, respectively (Conway *et al.*, 1983).

2.4.1.2 Terrestrial organisms

Ethylene oxide produces gene mutations in plant cells, including barley, rice and peas, exposed *in vitro* (Ehrenberg *et al.*, 1956, 1959; Blixt *et al.*, 1963; Shulovská *et al.*, 1969; Jana and Roy, 1975; Migliore *et al.*, 1982). Chromosome damage and sister chromatid exchange were observed in barley, wheat and spiderwort (*Tradescantia paludosa*) pollen (Smith and Lotfy, 1954; Ehrenberg *et al.*, 1956, 1959; Mackey, 1968; Moutschen-Dahmen *et al.*, 1968). Ehrenberg *et al.* (1956) reported a 5-fold increase in sterility caused by chromosomal aberrations in barley seeds treated at a gaseous ethylene oxide concentration of 1.5×10^6 mg/m^3 (80%) for 6 days. Second-generation chlorophyll gene mutations increased 33 times over controls under this treatment. Barley seeds soaked for 2 hours in solutions of 3084 and 11 894 mg/L induced second-generation chlorophyll gene mutations 3.7- and 13.8-fold over controls. Jana and Roy (1975) determined that for two genotypes of rice (*Oryza satica*), mutagenic efficiency decreased with increasing concentration of ethylene oxide. Concentrations ranged from 888 to 6167 mg/L, and exposure was for 8 hours.

In an examination of the control of pathogenic fungi (*Fusarium*, *Alternaria* and *Helminthosporium* spp.) on sorghum (*Sorghum vulgare* Pers.) through exposure to ethylene oxide, ethylene oxide applied to a filter paper disk at 8 mg/L was 92.3% effective in controlling fungal growth and 100% effective in inhibiting the viability of the sorghum seed (Raghunathan *et al.*, 1969). It should be noted that interpretation of this study is difficult because concentrations applied to the filter paper disks are not easily related to air or soil concentrations.

Although data are limited, insects appear to be relatively insensitive to atmospheric exposure to ethylene oxide. In 24-hour fumigation experiments, there was an increase in the control-corrected mortality rates from 24.5 to 98.6% in the khapra beetle (*Trogoderma granarium*) as the concentration of ethylene oxide increased from 1000 to 3000 mg/m^3, respectively. Reproduction of the surviving beetles did not differ significantly from that of untreated controls (Rajendran, 1982). Rajendran and Shivaramaiah (1985) studied the effect of 24-hour exposure to ethylene oxide at concentrations ranging from 250 to 1500 mg/m^3 on the reproductive rate of the lesser grain borer (*Rhyzopertha dominica* F.). Only concentrations above 500 mg/m^3 had any significant effect ($p = 0.01$) on reproductive rate. Chromosome damage has been observed in insects exposed to ethylene oxide, including observations of gene mutations in *Drosophila melanogaster* from a sex-linked recessive lethal test and *in vitro* evidence of chromosomal breaks and translocations (WHO, 1985).

No information is available describing the effects of ethylene oxide on birds or wild mammals. Laboratory animals are therefore used as surrogates for wildlife. The chronic reproductive effects in rats following inhalation of ethylene oxide at 183 mg/m^3, reported by Snellings *et al.* (1982b), are assumed to represent effects on wild rodent species and are selected as the most environmentally significant measurement endpoint for the assessment of the effects of ethylene oxide on the terrestrial environment (see also Section 2.4.3.5.1).

2.4.2 Abiotic atmospheric effects

Worst-case calculations to determine if ethylene oxide has the potential to contribute to the depletion of stratospheric ozone, ground-level ozone formation or climate change are presented below (Bunce, 1996).

The Ozone Depletion Potential (ODP) is 0, since ethylene oxide is not a halogenated compound (Bunce, 1996).

The Global Warming Potential (GWP) was calculated to be 0.031 (relative to the reference compound CFC-11, which has a GWP of 1), based on the following formula (Bunce, 1996):

$$\mathrm{GWP} = (t_{\mathrm{ethylene\ oxide}}/t_{\mathrm{CFC\text{-}11}}) \times (M_{\mathrm{CFC\text{-}11}}/M_{\mathrm{ethylene\ oxide}}) \times (S_{\mathrm{ethylene\ oxide}}/S_{\mathrm{CFC\text{-}11}})$$

where:

- $t_{\mathrm{ethylene\ oxide}}$ is the lifetime of ethylene oxide (0.60 years),
- $t_{\mathrm{CFC\text{-}11}}$ is the lifetime of CFC-11 (60 years),
- $M_{\mathrm{CFC\text{-}11}}$ is the molecular weight of CFC-11 (137.5 g/mol),
- $M_{\mathrm{ethylene\ oxide}}$ is the molecular weight of ethylene oxide (44.05 g/mol),
- $S_{\mathrm{ethylene\ oxide}}$ is the infrared absorption strength of ethylene oxide (2389/cm^2 per atmosphere, default), and
- $S_{\mathrm{CFC\text{-}11}}$ is the infrared absorption strength of CFC-11 (2389/cm^2 per atmosphere).

The Photochemical Ozone Creation Potential (POCP) was estimated to be 0.5 (relative to the value of an equal mass of the reference compound ethene, which has a POCP of 100), based on the following formula (Bunce, 1996):

$$\mathrm{POCP} = (k_{\mathrm{ethylene\ oxide}}/k_{\mathrm{ethene}}) \times (M_{\mathrm{ethene}}/M_{\mathrm{ethylene\ oxide}}) \times 100$$

where:

- $k_{\mathrm{ethylene\ oxide}}$ is the rate constant for the reaction of ethylene oxide with OH radicals (7.0×10^{-14} cm^3/mol per second),

- k_{ethene} is the rate constant for the reaction of ethene with OH radicals (8.5×10^{-12} cm^3/mol per second),
- M_{ethene} is the molecular weight of ethene (28 g/mol), and
- $M_{ethylene\ oxide}$ is the molecular weight of ethylene oxide (44.05 g/mol).

These figures suggest that the potential contribution of ethylene oxide to stratospheric ozone depletion and ground-level ozone creation is negligible. The potential to contribute to climate change is also considered to be minimal (Bunce, 1996).

2.4.3 Experimental animals and in vitro

2.4.3.1 Acute toxicity

Ethylene oxide is of low acute toxicity following inhalation, with 4-hour LC_{50}s of 1460, 835 and 960 ppm (2672, 1528 and 1757 mg/m^3) for rats, mice and dogs, respectively, being reported by Jacobson *et al.* (1956). Mortality of 80–100% was observed in male and female mice exposed to 800 ppm (1464 mg/m^3) ethylene oxide for 4 hours; no mortality was observed at the next lowest concentration (400 ppm [732 mg/m^3]) (NTP, 1987). LD_{50}s for ethylene oxide administered orally (in water) were 330 mg/kg-bw for male rats and 280 and 365 mg/kg-bw for female and male mice, respectively (Smyth *et al.*, 1941; Woodard and Woodard, 1971).

The lungs and nervous system are the principal organs affected following exposure to acutely toxic levels of ethylene oxide.

2.4.3.2 Short-term and subchronic toxicity

Available data on the repeated-dose toxicity of ethylene oxide are limited, being restricted primarily to inhalation studies in which animals were exposed to single concentrations.

Increased mortality was observed following the inhalation exposure of rats, mice, guinea pigs, rabbits and monkeys to concentrations of ethylene oxide ranging from 732 to 1500 mg/m^3 for 10 days to 8 weeks (Hollingsworth *et al.*, 1956; Jacobson *et al.*, 1956; Snellings, 1982; NTP, 1987). The exposure of rats to ethylene oxide at concentrations between 180 and 915 mg/m^3 for several weeks produced hematological effects (including decreases in hemoglobin and red blood cells and a reduction in the number of lymphocytes), changes in clinical chemistry, as well as histopathological alterations in various tissues, including the nasal mucosa, thymus and testes (Jacobson *et al.*, 1956; Snellings, 1982; Mori *et al.*, 1990). Effects observed in mice exposed to ethylene oxide at 810 mg/m^3 for 6 hours per day, 5 days per week, for 3 weeks included reduced body weight gain, poor coordination of the hind quarters, irregular breathing, convulsions and red urine. In both rats and mice, body weight gain was reduced following repeated exposure to levels of ethylene oxide as low as 90 mg/m^3 (6 hours per day, 5 days per week, for approximately 7 weeks) (Snellings, 1982).

Common effects observed following the subchronic exposure of rats to ethylene oxide have been hematological and metabolic disturbances. Reductions in hemoglobin concentration, hematocrit and red blood cell counts, accompanied by increases in reticulocytes, were observed in rats exposed to 915 mg ethylene oxide/m^3 for 6 hours per day, 3 times per week, for 13 weeks (Fujishiro *et al.*, 1990; Mori *et al.*, 1990). This exposure regimen also produced declines in the activities of glutathione reductase and creatine kinase in blood and various tissues (Katoh *et al.*, 1988, 1989; Matsuoka *et al.*, 1990; Mori *et al.*, 1990; Fujishiro *et al.*, 1991), as well as increased hepatic lipid peroxidation (Katoh *et al.*, 1988, 1989). Other effects observed in rats following subchronic exposure to ethylene oxide at concentrations ranging from 370 to 915 mg/m^3 included those on the nervous system (ataxia and axonal degeneration in the hind limbs and spinal cord) (Hollingsworth *et al.*, 1956; Ohnishi *et al.*, 1985, 1986; Matsuoka *et al.*, 1990; Mori *et al.*, 1990), disturbances in hepatic porphyrin-heme metabolism (Fujishiro *et al.*, 1990) and histopathological changes in the testes, kidneys and lungs (Hollingsworth *et al.*, 1956). Effects observed in mice exposed to ethylene oxide are similar to those in rats. Hematological changes, including decreases in red blood cell count, hemoglobin concentration, hematocrit, packed cell count, bone marrow cellularity and numbers of lymphocytes, have been observed in mice exposed (6 hours per day, 5 days per week, for 10 or 11 weeks) to ethylene oxide at concentrations of 425 or 467 mg/m^3 (Snellings *et al.*, 1984a; Popp *et al.*, 1986). Thymic lymphocytic necrosis, renal tubular necrosis and lymphocytic necrosis of the spleen have been reported after the exposure of mice to much higher concentrations (i.e., 1098 mg/m^3) for 6 hours per day, 5 days per week, for approximately 13 weeks; renal tubular degeneration was observed at concentrations as low as 183 mg/m^3 (NTP, 1987). Exposure to concentrations as low as 86 mg/m^3 reduced locomotor activity (Snellings *et al.*, 1984a).

In a limited, poorly reported study involving the exposure of rats, mice, rabbits, guinea pigs and monkeys to concentrations of ethylene oxide ranging from 90 to 640 mg/m^3, a reduction in growth was evident in all species at the highest concentration (statistical significance not reported) (Hollingsworth *et al.*, 1956). Atrophy of the hind leg muscles was observed in rabbits and monkeys after exposure to ≥370 mg ethylene oxide/m^3, for exposure periods ranging from 7 to 32 weeks (exact exposure periods not clearly specified) (Hollingsworth *et al.*, 1956). Guinea pigs exposed to 640 mg ethylene oxide/m^3 exhibited degeneration of the tubules of the testes, with "replacement fibrosis" as well as slight fatty degeneration in the adrenal cortex in females (Hollingsworth *et al.*, 1956). In another limited study, decreases in red blood cell count, hemoglobin and hematocrit were observed in two of three dogs exposed to 183 mg ethylene oxide/m^3 for 6 months (Jacobson *et al.*, 1956). No differences in hematological parameters (red or white blood cell counts, hematocrit, hemoglobin or white cell differential) were observed in rabbits exposed to 458 mg ethylene oxide/m^3 for 12 weeks, compared with unexposed controls (Yager and Benz, 1982).

In the only short-term study identified on the oral toxicity of ethylene oxide, there was a loss of body weight, gastric irritation and slight liver damage following exposure of rats to 100 mg ethylene oxide/kg-bw, 5 times per week, for a total of 15 doses in 21 days (Hollingsworth *et al.*, 1956). Information on the subchronic toxicity of ethylene oxide following ingestion was not identified.

2.4.3.3 Chronic toxicity and carcinogenicity

2.4.3.3.1 Chronic toxicity

Non-neoplastic effects associated with chronic exposure to ethylene oxide have not been investigated extensively, most studies having focussed on the carcinogenicity of this substance. In several investigations conducted with rats exposed to ethylene oxide for 2 years, significant reductions in body weight gain at concentrations as low as 60.4 mg/m^3 and decreased survival time at exposures of ≥92 mg/m^3 have been observed (Lynch *et al.*, 1984a,b; Snellings *et al.*, 1984b; Garman *et al.*, 1985; Garman and Snellings, 1986). Additional non-neoplastic effects observed at exposures of ≥92 mg ethylene oxide/m^3 include increased levels of aspartate aminotransferase in serum, reduced absolute kidney and adrenal weights, an increased incidence of inflammatory lesions in the lungs, nasal cavity, trachea and internal ear, proliferative and degenerative lesions in the adrenal cortex, as well as an increased incidence of multifocal mineralization of the posterior layers of the choroid/sclera portion of the eye (Lynch *et al.*, 1984a,b). Skeletal muscular atrophy (in the absence of sciatic nerve neuropathy) was noted following exposure to 183 mg ethylene oxide/m^3 (Lynch *et al.*, 1984a,b).

No exposure-related effects upon survival, body weight gain, clinical signs or other non-neoplastic endpoints (examined in a wide range of tissues) were observed in B6C3F$_1$ mice exposed to 92 or 183 mg ethylene oxide/m^3 for 2 years (NTP, 1987). (Notably, in subchronic studies with this strain of mice, neuromuscular screening tests revealed effects on locomotor activity at a concentration of 86 mg ethylene oxide/m^3 [Snellings *et al.*, 1984a].)

Monkeys exposed for 2 years to ≥92 mg ethylene oxide/m^3 developed axonal dystrophy in the nucleus gracilis of the medulla oblongata of the brain, along with demyelination in the distal portion of the fasciculus gracilis (Sprinz *et al.*, 1982; Lynch *et al.*, 1984b). Weight gain was significantly reduced following exposure to 183 mg ethylene oxide/m^3 (Lynch *et al.*, 1984a,b; Setzer *et al.*, 1996).

2.4.3.3.2 Carcinogenicity

Substance-related increases in a variety of tumour types have been observed in rodents exposed to ethylene oxide. In two studies, inhalation exposure increased the incidence of mononuclear cell leukemia[1] and gliomas of the brain in F344 rats of both sexes and of peritoneal mesotheliomas in male rats. In mice, increased incidences of alveolar/bronchiolar adenomas or carcinomas and Harderian gland papillary cystadenomas were observed in both sexes, while the incidences of malignant lymphomas, uterine and mammary gland adenocarcinomas and mammary gland adenocarcinomas or adenosquamous carcinomas (combined) were increased in females. An increase in squamous cell carcinomas of the forestomach was observed in female rats following the administration (by gavage) of ethylene oxide; the subcutaneous injection of ethylene oxide to female mice induced local fibrosarcomas.

In male (n = 80 per group) Fischer 344 rats exposed to 0, 50 or 100 ppm (0, 92 or 183 mg/m^3) ethylene oxide for 7 hours per day, 5 days per week, for 104 weeks, the incidence of mononuclear cell leukemia was 24/77, 38/79 ($p = 0.03$) and 30/76, respectively (Lynch *et al.*, 1984a,b). Among animals in the control, low- and high-concentration groups, the incidence of peritoneal mesotheliomas and mixed cell gliomas in brain tissue was 3/78, 9/79 and 21/79 ($p = 0.01$) and 0/76, 2/77 and 5/79 ($p < 0.05$), respectively. There was a significant concentration-related trend between the incidence of mesotheliomas and ethylene oxide exposure.

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[1] Mononuclear cell leukemias are unique to the F344 strain of rat. These tumours arise spontaneously, primarily in older animals. The exact etiology of this tumour type, including cell of origin, has not been definitively identified.

Similar results were observed when groups ($n = 120$ per sex) of male and female Fischer 344 rats were exposed to 0, 10, 33 or 100 ppm (0, 18.3, 60.4 or 183 mg/m^3) ethylene oxide for 6 hours per day, 5 days per week, for up to 2 years (Snellings *et al*, 1984b; Garman *et al.*, 1985; Garman and Snellings, 1986). The incidence of mononuclear cell leukemia (in animals sacrificed after exposure for 2 years) was (data from two control groups pooled) 13/97, 9/51, 12/39 and 9/30 (for males) and 11/116, 11/54, 14/48 and 15/26 ($p < 0.001$) (for females) in the control, low-, mid- and high-concentration groups, respectively. Trend analysis revealed a significant association for both sexes, although the increase was clearly concentration related only in females and was significantly different from the control group in females at the highest concentration only (i.e., 183 mg/m^3) (Snellings *et al.*, 1984b). Among males exposed to 0, 18.3, 60.4 or 183 mg ethylene oxide/m^3, the incidence of peritoneal mesotheliomas (in animals sacrificed after exposure for 2 years) was 2/97, 2/51, 4/39 and 4/30, respectively; trend analysis indicated a relationship between ethylene oxide exposure and tumour induction after adjustment for mortality (Snellings *et al.*, 1984b). Concentration-related increases in primary brain tumours (gliomas, malignant reticuloses and granular cell tumours) were observed in both sexes of rats exposed to ethylene oxide (Garman *et al.*, 1985; Garman and Snellings, 1986). Among animals in the control, low-, mid- and high-concentration groups, the incidence (expressed as number of animals with tumour/number alive at the time the first tumour was observed in any group) of such brain tumours (combined) was 1/181, 1/92, 5/85 ($p = 0.027$) and 7/87 ($p = 0.004$) (for males) and 1/188, 1/94, 3/92 and 4/80 ($p = 0.058$) (for females), respectively. The incidence of subcutaneous fibroma (15/58) was significantly increased in male rats in the highest exposure group (i.e., 183 mg/m^3) (Snellings *et al.*, 1984b). The increase in the incidence of mononuclear leukemia, mesothelioma and brain tumours in these animals occurred during the later stages of this study (i.e., after about 20–24 months of exposure to ethylene oxide) (Snellings *et al.*, 1984b; Golberg, 1986).

The chronic inhalation exposure of mice to ethylene oxide increased the incidence of tumours at sites different from those observed in rats. In groups ($n = 50$ per sex) of male and female B6C3F$_1$ mice exposed to 0, 50 or 100 ppm (0, 92 or 183 mg/m^3) ethylene oxide for 6 hours per day, 5 days per week, for 102 weeks, there was a significant concentration-related increase in the incidence of alveolar/bronchiolar carcinomas (NTP, 1987). Among animals in the control, low- and high-concentration groups, the incidence of alveolar/bronchiolar carcinomas was 6/50, 10/50 and 16/50 ($p = 0.019$) (for males) and 0/49, 1/48 and 7/49 ($p = 0.017$) (for females), respectively. For males and females exposed to 0, 92 or 183 mg ethylene oxide/m^3, the incidence of papillary cystadenoma within the Harderian gland was 1/43, 9/44 ($p = 0.012$) and 8/42 ($p = 0.012$) (males) and 1/46, 6/46 and 8/47 ($p = 0.033$) (females), respectively. In females, there were concentration-related increases in the incidence of malignant lymphomas of the hematopoietic system (9/49, 6/48 and 22/49 [$p = 0.005$]) and uterine adenocarcinoma (0/49, 1/47 and 5/49); the incidence of mammary adenocarcinoma and adenosquamous carcinoma (combined) was 1/49, 8/48 and 6/49, respectively (NTP, 1987).

In a study conducted with female A/J mice in which only the lungs were examined, a concentration-related increase in the incidence of pulmonary adenomas was observed following exposure (6 hours per day, 5 days per week) to 128 and 366 mg ethylene oxide/m^3 for 6 months (Adkins *et al.*, 1986).

In the only identified carcinogenicity study involving oral exposure, the intragastric administration of 7.5 or 30 mg ethylene oxide/kg-bw to female Sprague-Dawley rats twice weekly for 150 weeks produced a dose-related increase in the incidence of forestomach tumours (mainly squamous cell carcinomas) (Dunkelberg, 1982).

In female NMRI mice, the subcutaneous injection of ethylene oxide for 95 weeks (mean total doses up to 64.4 mg/mouse) yielded a significant dose-dependent increase in the number of tumours (i.e., sarcomas) at the site of injection (Dunkelberg, 1981). No skin tumours were observed in female ICR/Ha Swiss mice following the dermal application of approximately 100 mg ethylene oxide (10% in acetone) 3 times weekly for life (Van Duuren *et al.*, 1965).

2.4.3.4 Genotoxicity

Ethylene oxide is a potent alkylating agent that has displayed genotoxic activity in almost all studies (reviewed in IARC, 1994). In *in vitro* testing, it induced DNA damage and gene mutations in bacteria, yeast and fungi and gene conversion in yeast. In mammalian cells, observed effects have included gene mutations, micronucleus formation, chromosomal aberrations, cell transformation, unscheduled DNA synthesis, sister chromatid exchange and DNA strand breaks. Notably, Hallier *et al.* (1993) observed that the frequency of sister chromatid exchange in human peripheral blood lymphocytes exposed *in vitro* to ethylene oxide was higher in cells isolated from individuals expressing low levels of theta-class glutathione S-transferase (GSTT1), compared with the effect in cells from subjects expressing higher levels of this enzyme.

The results of *in vivo* studies on the genotoxicity of ethylene oxide have also been consistently positive (see IARC, 1994) following ingestion, inhalation or injection. *In vivo* exposure to ethylene oxide induced gene mutation at the hypoxanthine phosphoribosyl transferase (*Hprt*) locus in mouse and rat splenic T-lymphocytes; sister chromatid exchange was induced in lymphocytes from rabbit, rat and monkey, in bone marrow cells from mouse and rat and in rat spleen. Increases in the frequency of gene mutations in the lung (*lacI* locus) (Sisk *et al.*, 1997) and in T-lymphocytes (*Hprt* locus) (Walker *et al.*, 1997a) have been observed in transgenic mice exposed to ethylene oxide via inhalation, at concentrations similar to those employed in carcinogenesis bioassays with this species (NTP, 1987).

In male Big Blue® (*lacI* transgenic) B6C3F$_1$ mice exposed to 0, 50, 100 or 200 ppm (0, 92, 183 or 366 mg/m^3) ethylene oxide for 6 hours per day, 5 days per week, for 4 weeks, the observed mean (±SE) frequency of mutation at the *Hprt* locus in splenic T-lymphocytes was 2.2 (±0.03) × 10^{-6}, 3.8 (±0.5) × 10^{-6} ($p = 0.009$), 6.8 (±0.9) × 10^{-6} ($p = 0.001$) and 14.1 (±1.1) × 10^{-6} ($p < 0.001$), respectively (Walker *et al.*, 1997a). The frequency of *Hprt* mutations in splenic T-lymphocytes was reportedly increased (compared with unexposed controls) 5.0- to 5.6-fold in male F344 rats and (non-transgenic) male B6C3F$_1$ mice exposed to 200 ppm (366 mg/m^3) ethylene oxide for 6 hours per day, 5 days per week, for 4 weeks (Walker *et al.*, 1997b). The mean (±SD) frequency of *lacI* mutations in the lungs of male Big Blue® (*lacI* transgenic) B6C3F$_1$ mice exposed to 0 or 200 ppm (0 or 366 mg/m^3) ethylene oxide was 6.2 (±2.2) × 10^{-5} and 9.1 (±1.5) × 10^{-5} ($p < 0.05$), respectively (Sisk *et al.*, 1997). The mean (±SD) frequency of *lacI* mutations in the bone marrow, spleen and germ cells of these animals exposed to 0 or 200 ppm (0 or 366 mg/m^3) ethylene oxide was 2.5 (±1.1) × 10^{-5} and 4.7 (±2.1) × 10^{-5}, 4.2 (±0.7) × 10^{-5} and 5.4 (±3.2) × 10^{-5}, and 3.4 (±2.3) × 10^{-5} and 2.9 (±1.1) × 10^{-5}, respectively (Sisk *et al.*, 1997). In a recent study (reported in abstract form), a 5-fold increase (compared with unexposed controls) in the frequency of *lacI* mutations in bone marrow cells from Big Blue® (*lacI* transgenic) B6C3F$_1$ mice was observed following exposure to 200 ppm (366 mg/m^3) ethylene oxide, 6 hours per day, 5 days per week, for 48 weeks; however, no increase was observed following exposures either to lower concentrations or for shorter periods (Recio *et al.*, 1999).

In vivo exposure to ethylene oxide also induced heritable mutations or effects in germ cells in rodents (see IARC, 1994). Ethylene oxide induced dominant lethal effects in mice and rats and heritable translocations in mice. Dominant visible and electrophoretically detectable mutations were observed in the offspring of male mice exposed (by inhalation) to 200 ppm (366 mg/m^3) ethylene oxide for 6 hours per day, 5 days per week, for 7 weeks and then mated. This exposure regimen ensured that all progeny originated from sperm exposed during the entire spermatogenic process (Lewis *et al.*, 1986). In a study in which male (C3H × 101)F$_1$ mice were exposed by inhalation to 0, 165, 204, 250 or 300 ppm (0, 302, 373, 458, or 549 mg/m^3) ethylene oxide, 6 hours per day, 5 days per week, for 6 weeks, then daily for an additional 2.5 weeks, and subsequently mated to T-stock (or [SEC × 101]F$_1$) females, the percent dominant lethals ($p < 0.01$ at concentrations ≥373 mg/m^3, compared with controls) was 0 (0), 6 (8), 14 (13), 23 (24) and 60 (45), respectively (Generoso *et al.*, 1990). The frequency of translocation carriers ($p < 0.01$ at all concentrations, compared with controls) among the progeny of these groups of ethylene oxide-exposed male mice mated to T-stock (or [SEC × C57BL]F$_1$) females (data combined) was 1/2068 (0.05%), 32/1143 (2.8%), 52/1021 (5.1%), 88/812 (10.8%) and 109/427 (25.5%), respectively (Generoso *et al.*, 1990).

2.4.3.5 Reproductive and developmental toxicity

2.4.3.5.1 Effects on reproduction

Degeneration of the seminiferous tubules and germ cells, decreased epididymal weight, decreased sperm count and an increase in the percentage of abnormal sperm were observed in Wistar rats exposed to ≥458 mg ethylene oxide/m^3 for 13 weeks (Mori *et al.*, 1989, 1991). When abnormal sperm heads were classified into immature and teratic types, the frequency of teratic types was increased at exposures of ≥92 mg/m^3, although it was not concentration dependent (Mori *et al.*, 1991). Decreased relative testicular weight was observed in rats after exposure to 915 mg ethylene oxide/m^3 (Mori *et al.*, 1989). In a limited study in rats, slight degeneration of the tubules in the testes was observed after exposure to 370 mg ethylene oxide/m^3 for 25–32 weeks (Hollingsworth *et al.*, 1956). Embryotoxic and fetotoxic effects have been observed in reproductive studies with rats after exposure of the dams via inhalation to concentrations of ethylene oxide between 183 and 275 mg/m^3, prior to mating and throughout gestation. These effects included a decrease in the number of implantation sites per pregnant female, an increase in the incidence of resorptions, a decrease in the median number of pups born on day 0 postpartum per litter, as well as a lower ratio of the number of fetuses born to the number of implantation sites per female (Hackett *et al.*, 1982; Snellings *et al.*, 1982a,b; Hardin *et al.*, 1983). Under these exposure conditions, adverse effects on the dams were not observed (based simply upon clinical appearance and demeanor).

Reproductive effects in mice are similar to those observed in rats. After exposure of female hybrid mice to 300 or 1200 ppm (549 or 2196 mg/m^3) ethylene oxide for a period prior to mating, an increase in the number of resorption bodies and reductions in the number of implants per female and in the number of living embryos per female were observed (Generoso *et al.*, 1987). Exposure of Swiss-Webster mice to 366 mg ethylene oxide/m^3 for 5 days produced a concentration-related increase in the percentage of abnormal sperm (Ribeiro *et al.*, 1987). A slight (7%) decline in absolute but not relative testicular weight was observed in B6C3F$_1$ mice after exposure to 86 mg ethylene oxide/m^3 for 10 weeks; however, no histological changes were observed in this tissue (Snellings *et al.*, 1984a).

A decline in sperm count and motility was observed in monkeys exposed to concentrations of ethylene oxide as low as 92 mg/m^3 for 24 months (Lynch *et al.*, 1984b,c).

2.4.3.5.2 Developmental toxicity

Exposure of Sprague-Dawley rats to a maternally toxic concentration of 275 mg ethylene oxide/m^3 either prior to mating and throughout gestation or only during various stages of gestation resulted in reduced fetal body weight and crown-rump length, as well reduced skeletal ossification (Hackett *et al.*, 1982; Hardin *et al.*, 1983). In a study with Fischer 344 rats, reduced fetal body weights were observed when the dams were exposed only during the period of organogenesis to 183 mg ethylene oxide/m^3, a concentration having no overt toxic effects on the dams (Snellings *et al.*, 1982a). Repeated brief exposures of pregnant Sprague-Dawley rats during gestation to 1464 or 2196 mg ethylene oxide/m^3 produced a decline in fetal body weight (at both concentrations) and maternal toxicity (reduced body weight gain) at 2196 mg/m^3 (Saillenfait *et al.*, 1996); however, there was no evidence of teratogenicity.

In offspring of female hybrid mice exposed to 2196 mg ethylene oxide/m^3 at various intervals shortly after mating, there was a range of congenital malformations, including omphalocoele, hydrops, eye defects, open thorax, cardiac defects, cleft palate and tail and limb defects (Generoso *et al.*, 1987; Rutledge and Generoso, 1989). Increases in the numbers of mid-gestational and late fetal deaths and offspring that did not reach weaning were also observed (Generoso *et al.*, 1987; Rutledge and Generoso, 1989; Rutledge *et al.*, 1992). In the offspring of female mice exposed to ≥1647 mg ethylene oxide/m^3 for brief periods shortly after mating, skeletal ossification was reduced and the incidence of axial skeletal anomalies and cleft sternum was increased (Polifka *et al.*, 1991, 1992).

The intravenous administration of 150 and 18 mg ethylene oxide/kg-bw per day during gestation to mice and rabbits, respectively, produced fetotoxic effects as well as effects in the dams (LaBorde and Kimmel, 1980; Jones-Price *et al.*, 1983). The intraperitoneal administration of a single dose of 125 mg ethylene oxide/kg-bw to pregnant hybrid mice during either the zygotic or the embryonic period reduced post-implantation survival and increased the incidence of skeletal abnormalities (information concerning maternal toxicity was not provided) (Polifka *et al.*, 1996).

2.4.3.6 Neurological effects

Effects on the nervous system have been observed frequently in laboratory animals exposed to ethylene oxide. The paralysis observed in some animals was reversed upon the cessation of exposure (Hollingsworth *et al.*, 1956). Poor coordination of the hind quarters was observed in rats and mice following exposure to 810 mg ethylene oxide/m^3 for 7–8 weeks (Snellings, 1982). In subchronic or chronic studies in rats exposed to 458–915 mg ethylene oxide/m^3, there was a range of neurological effects, including awkward or ataxic gait, paralysis and atrophy of the muscles of the hind limbs, accompanied in some cases by pathological evidence of axonal degeneration of myelinated fibres in nerves of the hind legs (Hollingsworth *et al.*, 1956; Ohnishi *et al.*, 1985, 1986; Matsuoka *et al.*, 1990; Mori *et al.*, 1990). Abnormal posture during gait and reduced locomotor activity were also observed in mice after exposure to ethylene oxide at concentrations ranging from 86 to 425 mg/m^3, for 6 hours per day, 5 days per week, for 10 or 11 weeks (Snellings *et al.*, 1984a); effects on various reflexes (righting, tail pinch, toe pinch) were also noted at the highest concentration examined (i.e., 425 mg/m^3).

In a limited, poorly reported study in rabbits and monkeys, paralysis of the hind limbs was observed in both species accompanied by atrophy of the leg muscles, following exposure to $\geq$370 mg ethylene oxide/m^3 for periods ranging from 7 to 32 weeks (exact exposure periods were not clearly specified) (Hollingsworth *et al.*, 1956).

In two studies of male cynomolgus monkeys exposed to 92 or 183 mg ethylene oxide/m^3 for 2 years (Sprinz *et al.*, 1982; Lynch *et al.*, 1984b), histological alterations in the axons within the nucleus gracilis of the medulla oblongata and demyelination of the distal portion of the fasciculus gracilis within the medulla were observed.

2.4.3.7 Toxicokinetics and mode of action

Information on the kinetics and metabolism of ethylene oxide has been derived primarily from studies conducted with laboratory animals exposed via inhalation, although some limited data from humans have been identified. In animals and humans, there are two routes of ethylene oxide catabolism, both of which are considered to be detoxification pathways. The first involves hydrolysis to ethylene glycol, with subsequent conversion to oxalic acid, formic acid and carbon dioxide. The second involves conjugation with glutathione, with subsequent metabolic steps yielding S-(2-hydroxyethyl)cysteine [S-(2-carboxymethyl)cysteine] and their N-acetylated derivatives (i.e., N-acetyl-S-(2-hydroxyethyl)cysteine [and N-acetyl-S-(2-

carboxymethyl)cysteine]) (Wolfs *et al.*, 1983; WHO, 1985; ATSDR, 1990; Popp *et al.*, 1994). Based upon available data, the route involving conjugation with glutathione appears to predominate in rats and mice; in larger species (rabbits, dogs), the conversion of ethylene oxide is primarily via hydrolysis through ethylene glycol (Jones and Wells, 1981; Martis *et al*, 1982; Gérin and Tardif, 1986; Tardif *et al.*, 1987).

Ethylene oxide is a substrate for the human GSTT1 enzyme (Hallier *et al.*, 1993; Pemble *et al.*, 1994; Hayes and Pulford, 1995). There appears to be no ***qualitative*** difference in the metabolism of ethylene oxide between laboratory animals (i.e., rodents) and humans. Brown *et al.* (1996) indicated that approximately 50% and 30% of total urinary metabolites arising from inhaled ethylene oxide would be derived via the glutathione conjugation pathway in mice and rats, respectively. Levels of GSTT1 enzyme activity decrease in the order mice > rats > humans.[2] Brown *et al.* (1996) reported that the specific activity of GSTT1 (using ethylene oxide as the substrate) in the liver and kidney was greater in mice than in rats. The specific activity of GSTT1 (measured using dichloromethane as the substrate) in human tissues appears to be about 10% of that in mice (Reitz *et al.*, 1989; Hashmi *et al.*, 1994). ***In situ*** hybridization studies have indicated that differences in enzymatic activity are likely attributable (at least in part) to the differential expression of the GSTT1 gene among mice, rats and humans (Mainwaring *et al.*, 1996).

Ethylene oxide is an electrophilic agent that alkylates nucleophilic groups in biological macromolecules, including DNA and proteins. In hemoglobin, for example, adducts can be formed at cysteine residues, N-terminal valine, as well as N^{τ}- and N^{π}-histidine (Segerbäck, 1990). Since ethylene oxide is formed during the metabolism of ethylene, a natural body constituent, endogenous as well as exogenous sources of ethylene and ethylene oxide contribute to background alkylation of proteins such as hemoglobin and albumin, as well as DNA (Bolt, 1996). N-(2-hydroxyethyl)valine (HEVal) and hydroxyethylhistidine (HEHis) adducts have been frequently monitored in tissues of workers exposed to ethylene oxide in occupational settings (see IARC, 1994). Background levels of HEVal in non-smokers ranged from 9 to 188 pmol/g globin (Törnqvist *et al.*, 1986, 1989; Bailey *et al.*, 1988; Hagmar *et al.*, 1991; Sarto *et al.*, 1991; Tates *et al.*, 1991, 1992; van Sittert et al., 1993; van Sittert and van Vliet, 1994; Farmer *et al.*, 1996; Granath *et al.*, 1996). Ethylene oxide binding to DNA results primarily in the formation of 7-(2-hydroxyethyl)guanine (7-HEGua) (Föst *et al.*, 1989; Li *et al.*, 1992); other adducts have also been identified at much lower levels. In DNA extracted from the lymphocytes of unexposed individuals, mean background levels of 7-HEGua ranged from 2 to 8.5 pmol/mg DNA (Föst *et al.*, 1989; Bolt *et al.*, 1997). Although these levels were similar to those measured in rodents not exposed to ethylene oxide (Föst *et al.*, 1989; Walker *et al.*, 1992), Wu *et al.* (1999a), using a more sensitive technique, recently reported that human tissue contains 10- to 15-fold higher levels of endogenous 7-HEGua than rodent tissue.

Among rodent species, there are clear quantitative differences in metabolism. Clearance of ethylene oxide from the blood (and other tissues) was approximately 3- to 4-fold faster in mice than in rats; peak levels of ethylene oxide in the muscle and brain of rats and mice were similar (Brown *et al.*, 1996). GSTT1 activity was highest in the liver, followed by the kidney and testes. Rat brain and rat and mouse lung contained small amounts of activity, compared with other tissues (enzyme activity in mouse brain was not examined).[3] Levels of ethylene oxide in the testes of rats were 20% of those in other tissues, while in mice, levels in the testes were 50% of those measured in other tissues (Brown *et al.*, 1996). In mice, half-lives for the elimination of 7-HEGua in DNA from a variety of tissues (brain, lung, spleen, liver and testes) were 1.5- to 3.9-fold lower than in rats (Walker *et al.*, 1992). In both rats and mice, substantive depletion of glutathione pools has been observed following acute exposure to high levels (i.e., ≥300 ppm [549 mg/m^3]) of ethylene oxide (McKelvey and Zemaitis, 1986; Brown *et al.*, 1998), although it should be noted that increases in tumour incidence have been observed at lower concentrations.

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[2] Although sites at which tumours occur in rats and mice vary, carcinogenic potency is generally greater in rats than in mice.

It is likely that toxicological effects associated with exposure to ethylene oxide arise primarily as a result of its direct alkylation of biological macromolecules (i.e., nucleic acids, proteins). *In vivo* exposure to ethylene oxide induced mutations (5- to 5.6-fold) at the *Hprt* locus in splenic T-lymphocytes in rats and mice (Walker *et al.*, 1997a,b). A statistically significant (i.e., $p < 0.05$) increase (1.5-fold) in the frequency of *lacI* mutation was observed in the lungs of transgenic mice exposed to 200 ppm (366 mg/m^3) ethylene oxide (Sisk *et al.*, 1977); the increased frequency of *lacI* mutations in the bone marrow and spleen of these animals (1.9- and 1.3-fold, respectively) was not statistically different from the unexposed controls. Currently, there is no clear evidence of a relationship between the mutagenic response observed at these two "indicator" loci and the species- and tissue-specific carcinogenicity of ethylene oxide. Molecular analysis of ethylene oxide-induced mutations at the *HPRT* locus in human diploid fibroblasts exposed *in vitro* revealed that a high proportion involved large deletions of this gene (Bastlová *et al.*, 1993).

A potential role of the formation of 7-HEGua in contributing to the carcinogenic response has been the focus of many studies, this adduct having been identified in both humans and laboratory animals. In reports by Walker *et al.* (1992) and Wu *et al.* (1999b), F344 rats and $B6C3F_1$ mice were exposed (via inhalation for 6 hours per day, 5 days per week, for 4 weeks) to concentrations of ethylene oxide similar to those used in previous carcinogenicity bioassays involving these strains (Lynch *et al.*, 1984a,b; Snellings *et al.*, 1984b; Garman *et al.*, 1985; Garman and Snellings, 1986; NTP, 1987). Slightly higher levels of 7-HEGua were measured in tissues (lung, spleen, brain, liver) from rats than from mice; within each species, similar levels of the adduct were measured in the lung, spleen, brain and liver. Since an increased incidence of brain tumours has been observed in rats but not in mice exposed to ethylene oxide and an increased incidence of lung tumours has been observed in mice but not in rats exposed to this substance, the results provided by Walker *et al.* (1992) and Wu *et al.* (1999b) point to no obvious relationship between the *overall level* of 7-HEGua within various tissues and the observed species-specific carcinogenic response. The potential roles of this and/or other ethylene oxide-induced DNA adducts as well as other factors in mediating the carcinogenicity of ethylene oxide have not been defined.

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[3] These results are consistent with the observation of tumours in mouse lung and rat brain, if GSTT1 activity is the critical determinant, but not with the lack of observation of tumours in rat lung.

2.4.4 Humans

2.4.4.1 Non-neoplastic effects

2.4.4.1.1 Irritation and sensitization

Exposure to ethylene oxide vapour can cause irritation of the eyes, nose and throat; however, the sensory warning signs of the chemical are poor (ATSDR, 1990). Brief exposure of workers to the chemical produced irritation of the mucous membranes of respiratory passages, which led to bronchitis, pulmonary edema and, in one case, emphysema (Thiess, 1963). Mild irritation of the skin has been reported after contact with aqueous solutions of ethylene oxide as low as 1% (Sexton and Henson, 1949). Dermal injury is characterized by edema and erythema, occurring 1–5 hours after exposure, followed by the formation of vesicles. The magnitude of the injury is dependent upon both the duration of contact and the concentration to which the individual is exposed (WHO, 1985). Dermal irritation has also been observed after contact with ethylene oxide-sterilized materials and clothing, such as surgical dressings and tubing, face masks, gloves, boots, surgical gowns and overalls (Royce and Moore, 1955; Marx *et al.*, 1969; Hanifin, 1971; Biro *et al.*, 1974; LaDage, 1979; Bommer and Ritz, 1987; Fisher, 1988; Lerman *et al.*, 1995).

Ethylene oxide is considered a good sensitizing agent, owing to its strong reactivity with various chemical groups. Type I (anaphylaxis) and Type IV (contact dermatitis) hypersensitivity reactions have been observed in individuals exposed to ethylene oxide. Anaphylactic reactions (ranging from mild to severe) have been noted among patients undergoing various forms of dialysis (e.g., hemodialysis, peritoneal dialysis, plasmapheresis, plateletpheresis) involving equipment sterilized by exposure to ethylene oxide (reviewed in Bommer and Ritz, 1987). Asthmatic reactions may occur either alone or in combination with anaphylactic events; case reports of occupational asthma attributed to ethylene oxide exposure have appeared (Dugue *et al.*, 1991; Verraes and Michel, 1995). Reports of contact dermatitis attributed to ethylene oxide are not uncommon; however, the clinical diagnosis should distinguish a true allergic reaction from the normally irritative effects of this chemical.

2.4.4.1.2 Reproductive effects

In studies of female sterilization workers and one study involving paternal exposure to ethylene oxide, increased risks of adverse pregnancy outcome, most often spontaneous abortion, have been reported. In one study, Hemminki *et al.* (1982) determined the incidence of spontaneous abortion among Finnish hospital staff who had used ethylene oxide, glutaraldehyde and formaldehyde for instrument sterilization. All sterilizing staff employed in Finnish hospitals in 1980 were included in the analysis, with a total of 1443 pregnancies (545 workers exposed during pregnancy). Measurements carried out in 24 Finnish hospitals since 1976 revealed 8-hour, time-weighted-average (TWA) exposures ranging from 0.1 to 0.5 ppm (0.2 to 0.9 mg/m^3) ethylene oxide, with peak concentrations up to 250 ppm (458 mg/m^3). However, no measurements were taken during the study, and the concentrations of ethylene oxide may have been higher prior to 1976. When the pregnancies of the sterilizing staff were analysed according to employment at the time of conception, the rate of spontaneous abortion was significantly ($p < 0.001$) increased in the exposed (15.1%) versus the unexposed (4.6%) group. When the associations between ethylene oxide and the different sterilizing agents were analysed, only exposure to ethylene oxide during early pregnancy was related to an increased frequency of spontaneous abortion (adjusted rate of 16.1% in exposed versus 7.8% in unexposed workers; $p < 0.01$). Hospital discharge records revealed a similar pattern, with spontaneous abortion rates of 22.6% (significantly higher than controls, $p < 0.05$), 9.9% and 9.2% in sterilizing workers exposed to ethylene oxide, unexposed workers and controls, respectively. In a subsequent analysis, only pregnancies that began during hospital employment were analysed in all groups, with controls chosen from the same hospitals (Hemminki *et al.*, 1983). The rate of spontaneous abortion remained significantly higher ($p < 0.05$) among the pregnancies associated with exposure to ethylene oxide (20.4%) compared with controls (11.3%).

Rowland *et al.* (1996) examined the occurrence of spontaneous abortion and pre- and post-term delivery in relation to ethylene oxide exposure among 7000 randomly selected dental assistants (aged 18–39) identified from the 1987 dental assistant registry in California. The most recent pregnancy outcome was chosen for analysis to maximize recall of pregnancy and exposure information, with 1320 women who provided information on age and ethylene oxide exposure contributing to the analysis. A total of 32 women reported ethylene oxide exposure during pregnancy; no quantitative measures or details on timing of exposure during pregnancy were available. The age-adjusted relative risk of spontaneous abortion among ethylene oxide-exposed women was 2.5 (95% confidence interval [CI] = 1.0–6.3); the relative risks of pre-term births (21–37 weeks) and post-term births (≥42 weeks) were 2.7 (95% CI = 0.8–8.8) and 2.1 (95% CI = 0.7–5.9), respectively. Using a logistic model, ethylene oxide-exposed women were 2.7 times (95% CI = 1.2–6.1) more likely to have any of the three adverse pregnancy outcomes after adjusting for age. Adjustment for unscavenged nitrous oxide exposure, high amalgam use and smoking yielded a relative risk of 2.1 (95% CI = 0.7–5.7).

In the only identified study in which the effect of paternal exposure to ethylene oxide on reproductive outcome was assessed, Lindbolm *et al.* (1991) reported a significantly ($p < 0.05$) increased risk of spontaneous abortion (odds ratio [OR] = 4.7; 95% CI = 1.2–18.4) among Finnish women whose partners had been exposed to ethylene oxide. In total, 99 186 pregnancies were included in the analysis. Paternal exposure to ethylene oxide was based upon the job and industry in which the men were employed; quantitative data on exposure were not available, and the numbers of spontaneous abortions ($n = 3$) and pregnancies ($n = 10$) in the paternal ethylene oxide-exposed group were small. Other potential confounding factors, such as previous abortions and alcohol and tobacco consumption, were not considered in the analysis.

2.4.4.1.3 Neurological effects

Sensorimotor polyneuropathy was reported for a number of cases following acute or chronic exposure to ethylene oxide (exposure concentrations, when reported, ranged from 4.2 to >700 ppm [7.7 to >1281 mg/m^3]) (Gross *et al.*, 1979; Finelli *et al.*, 1983; Kuzuhara *et al.*, 1983;

Zampollo *et al.*, 1984; Schroder *et al.*, 1985; Fukushima *et al.*, 1986; Ristow and Cornelius, 1986; Crystal *et al.*, 1988). Amelioration of the symptoms following the cessation of exposure has been commonly observed. Abnormally low nerve conduction velocities were observed in some cases, along with numbness and weakness in the extremities, slow and clumsy alternating hand movements, decreased muscle stretch reflexes in extremities, heel-shin ataxia and unsteady and wide-based gait. In individuals exposed to >700 ppm (1281 mg/m^3) ethylene oxide, sural nerve biopsies revealed axonal degeneration with mild changes in the myelin sheath; muscle biopsies revealed degeneration atrophy (Kuzuhara *et al.*, 1983). Effects on the central nervous system (e.g., seizures) have been observed following acute exposure to 500–700 ppm (915–1281 mg/m^3) ethylene oxide (Gross *et al.*, 1979; Salinas *et al.*, 1981).

Chronic occupational exposure to ethylene oxide has been associated with impaired performance in neuropsychological testing (most often on tests of psychomotor skills) and, in one study, with reduced peripheral nerve conduction velocity. However, in all identified studies, the numbers of subjects, often of unknown comparability, were small. In eight females who had worked at a hospital with or in the proximity of ethylene oxide gas sterilizers for 5–20 years (mean 11.6 years; TWA in breathing zone up to 3 ppm [5.5 mg/m^3]), performance was poor on all psychometric tests and significantly less accurate in the hand–eye coordination test ($p = 0.03$) than that in unexposed hospital workers or members of the same union matched for age and sex (Estrin *et al.*, 1987). A significant correlation was observed between decreasing performance on the continuous performance test and years of exposure to ethylene oxide, after controlling for age ($r = 0.67$; $p \pm 0.05$) (Estrin *et al.*, 1987). Subsequently, in 10 female hospital workers with chronic exposure to ethylene oxide (breathing zone levels up to 250 ppm [458 mg/m^3]), the proportion of individuals with bilaterally reduced ankle reflexes was higher ($p \pm 0.05$) than in the same number of unexposed controls (Estrin *et al.*, 1990). There was no difference with respect to sural and peroneal amplitudes and velocities, nor were there any significant differences on neuropsychological tests of cognition requiring verbal ability. Compared with the controls, the ethylene oxide-exposed group performed poorly on the Trails A test ($p = 0.04$), the cancellation test ($p = 0.06$) and the computerized finger tapping test ($p = 0.009$), all of which assess psychomotor skills. The exposed group had a statistically significant lower P300 amplitude, which has been associated with cognitive dysfunction (Estrin *et al.*, 1990).

Neuropsychological effects possibly associated with chronic exposure to ethylene oxide were examined in a cross-sectional study of 22 male and female hospital supply workers exposed to low levels of ethylene oxide and in 24 unexposed controls from local hospitals (Klees *et al.*, 1990). The 8-hour TWA concentration was 4.7 ppm (8.6 mg/m^3) ethylene oxide. Significantly more individuals in the ethylene oxide-exposed group ($p < 0.05$) were classified (by two neuropsychologists) as “impaired” ($n = 5$) compared with the controls ($n = 1$), following evaluation using a neuropsychological screening battery designed to assess a spectrum of neuropsychological functions (including memory, verbal, visual–spatial and psychomotor functions) considered likely to be affected by neurotoxic exposures.

2.4.4.1.4 Genetic effects

Increases in chromosomal aberrations in peripheral blood lymphocytes have been consistently reported in studies of workers exposed to concentrations of ethylene oxide of ≥5 ppm (9.2 mg/m^3) (Table 4). Effects observed at lower concentrations (i.e., <5 ppm [9.2 mg/m^3]) have been mixed.

Significant increases in the frequency of sister chromatid exchange have also been observed among individuals exposed to elevated levels of ethylene oxide (i.e., usually ≥5 ppm [9.2 mg/m^3]). Studies of individuals exposed to lower levels (i.e., <0.5 ppm [0.9 mg/m^3]) have yielded mixed results. In some studies, increases in the frequency of sister chromatid exchange have been observed to persist after exposure had ceased. Effects related to the concentration or duration of exposure to ethylene oxide have been observed in a number of studies.

In some studies, the frequency of micronuclei in peripheral blood was increased in workers exposed to relatively high (2–33 ppm [3.7–60.4 mg/m^3]) levels of ethylene oxide (Tates *et al.*, 1991; Ribeiro *et al.*, 1994). However, in the majority of the studies involving exposures to lower levels, no effect on the frequency of micronuclei was observed. Apparent inconsistencies in the data could reflect the influence of peak exposures, differences in exposure duration or smoking status.

In a study involving small numbers (i.e., n = 4–12 per group, depending upon exposure group) of non-smoking males and females exposed to ethylene oxide through the sterilization of medical equipment, Fuchs *et al.* (1994) reported statistically significant ($p < 0.05$), concentration-dependent increases (1.5- and 2.2-fold, respectively) in single-strand DNA breaks in peripheral mononuclear blood cells obtained from individuals exposed to (4-hour TWA) ethylene oxide concentrations of 0.1–0.49 mg/m^3 and 0.5–2.0 mg/m^3, compared with workers exposed to levels below 0.1 mg/m^3. A 1.5-fold increase in DNA single-strand breaks in cells from workers exposed to >2 mg ethylene oxide/m^3 was not significantly different (i.e., $p > 0.05$) from the number observed in cells from workers exposed to <0.1 mg/m^3. The group of non-smokers could be divided into subgroups having a "higher" or "lower" sensitivity to ethylene oxide.

2.4.4.1.5 Other non-neoplastic effects

Only a limited range of other non-neoplastic effects has been investigated in humans exposed to ethylene oxide. Hematological changes were observed among a group of 59 women exposed to ethylene oxide released from sterilizers while employed at nine hospitals in the United States and one in Mexico (Schulte *et al.*, 1995). Exposure was classified as none, low or high, based on mean 4-month cumulative exposure categories of 0, >0–32 or >32 ppm-hour, respectively. Mean 8-hour TWA exposures in the U.S. hospitals were 0.08 ppm (0.15 mg/m^3) (range = 0–0.55 mg/m^3) and 0.17 ppm (0.31 mg/m^3) (range = 0.24–0.55 mg/m^3) for the low- and high-exposure categories, respectively; the corresponding measurements in the Mexican hospital were 0.02 ppm (0.04 mg/m^3) and 0.54 ppm (0.99 mg/m^3) (range = 0.5–2.5 mg/m^3), respectively. Among the U.S. workers, hematocrit and hemoglobin levels were reduced (not statistically significant) in the high-exposure group, compared with the unexposed controls; the levels were significantly lower in the high-exposure group when compared with the low-exposure group ($p = 0.03$ and 0.02 for hemoglobin and hematocrit levels, respectively). Compared with unexposed controls, U.S.

workers in the high-exposure group exhibited a statistically significant ($p = 0.04$) increase in the percentage of lymphocytes and a reduction ($p = 0.03$) in the percentage of neutrophils in the blood. Among the Mexican workers, an exposure-related increase (not statistically significant) in the percentage of neutrophils in the blood was observed.

Hematological changes were not observed either in a group of 36 male workers employed at an ethylene oxide manufacturing plant with estimated 8-hour TWA exposures below 0.05 ppm (0.09 mg/m^3) (van Sittert *et al.*, 1985) or in a group of 84 male workers involved in the manufacture of ethylene oxide who were exposed to estimated concentrations of <1 ppm (1.83 mg/m^3) (Currier *et al.*, 1984).

The prevalence of lens opacities and cataracts was assessed in a group of 55 workers exposed to ethylene oxide at five hospitals in Paris, France (Deschamps *et al.*, 1990). Airborne concentrations of ethylene oxide ranged from 0.06 ppm (0.11 mg/m^3) during a 97-minute exposure to 39 ppm (71 mg/m^3) during a 2.5-minute exposure. Initial results revealed a greater prevalence of lens opacities among individual over 45 years of age, and therefore comparisons were limited to this age group. There was no difference between the exposed and control groups in the prevalence (19/21 exposed; 10/16 unexposed), location, importance or type of lens opacities observed. Cataracts were observed in six exposed individuals (all over 45 years of age except one who was 44 years), compared with none in the control group ($p < 0.05$).

2.4.4.2 Cancer

Associations between occupational exposure to ethylene oxide and various types of cancer have been examined in a number of epidemiological studies. A summary of the risk measures for selected cancers (stomach, pancreas, brain, hematopoietic system) is presented in Table 5.

In a cohort study of 709 ethylene oxide production and sterilization workers in Sweden, mortality due to leukemia (standardized mortality ratio [SMR] = 921; 7 observed deaths), blood and lymphatic cancer (SMR = 459; 9 observed deaths) and stomach cancer (SMR = 546; 10 observed deaths) was increased (Hogstedt, 1988). The greatest excess mortality was observed in operators and repairmen employed in an old production plant where ethylene oxide had been synthesized by the chlorohydrin method from 1941 to 1947 (mostly in an enclosed building), although there were no trends by duration of employment (<10 years, >10 years). Ethylene oxide exposure levels in all of the facilities were estimated to have been relatively high in the early years (average exposure levels were estimated to have been 14 ppm [26 mg/m^3] between 1941 and 1947 at the plant producing ethylene oxide by the chlorohydrin method; however, peaks above the odour threshold of 400 ppm [732 mg/m^3] had been reported).

Greenberg *et al.* (1990) conducted a study of 2174 workers employed at two ethylene oxide production plants in the United States, for which a 10-year update of this cohort, which excluded 278 chlorohydrin workers, was reported by Teta *et al.* (1993). Comparisons were with both the general population and unexposed workers in the plants. In this cohort, there were no statistically significant increases in deaths from any cause for the entire cohort; SMRs for cancer of the stomach, pancreas, brain and nervous system, and leukemia and aleukemia were 160 (95%

CI = 69–315; 8 observed deaths), 61 (95% CI = 17–156; 4 observed deaths), 150 (95% CI = 55–327; 6 observed deaths), and 106 (95% CI = 35–248; 5 observed deaths), respectively (Teta *et al.*, 1993). Although no increased mortality was observed among men from the high-exposure departments (expected number of deaths not reported), a statistically significant excess of deaths due to stomach cancer was observed in the intermediate-exposure group (SMR = 364; 95% CI = 102–957; 4 observed deaths); an increase (not statistically significant) was also observed in the low-exposure group (SMR = 222; 95% CI = 61–575; 4 observed deaths). When risks associated with duration of assignment were examined, there were no significant trends for all cancers, leukemia, pancreatic, brain or stomach cancers, although the numbers of deaths from cancer at any site were small. However, the relative risk for stomach cancer (2.77; 95% CI = 1.11–6.93; 5 observed deaths) was significantly elevated for those exposed from 2 to 9 years. An analysis of the 278 ethylene chlorohydrin production workers, considered to have only low, intermittent exposure to ethylene oxide, revealed SMRs for deaths due to digestive and peritoneal, pancreatic, respiratory and lymphatic/hematopoietic cancers of 143 (95% CI = 74–250; 12 observed deaths), 492 (95% CI = 158–1140; 8 observed deaths), 136 (95% CI = 76–224; 15 observed deaths) and 294 (95% CI = 127–580; 8 observed deaths), respectively (Benson and Teta, 1993).

TWA exposures were estimated over four time periods and three exposure intensity categories (low, medium, high). Average exposures in the most recent time period were based on industrial hygiene monitoring conducted in the plants and were inferred for earlier time periods based on exposure levels in similar manufacturing operations during the period of interest. A separate age-dependent exposure history was developed for each worker, based on the worker's assignments and estimated exposure levels (i.e., low, medium, high).

While there were no ***quantitative*** estimates of individual exposure in this investigation (assignments were to low, medium or high exposure only), the length of follow-up was among the longest in any study (mean duration of follow-up, 27.2 years; mean length of exposure, 5.4 years). Workers were exposed to a variety of other chemicals (approximately 26, including butadiene and benzene) (Shore *et al.*, 1993).

In the largest single cohort studied to date, Steenland *et al.* (1991) examined mortality in 18 254 male and female workers exposed to ethylene oxide at 14 plants producing sterilized medical supplies and spices in the United States. Comparisons were with the U.S. general population. A more detailed analysis of exposures in this cohort was subsequently conducted by Stayner *et al.* (1993), being restricted to workers from 13 of the 14 original facilities having adequate information for estimating historical exposures. The database on which these exposure estimates were based was collected in the course of walkthrough surveys of 36 companies in the medical supplies and spice industries and in-depth sampling surveys of 2 of these 36 companies; the database included 2350 individual TWA exposure values acquired from 18 facilities between 1976 and 1985 (Greife *et al.*, 1988). Arithmetic mean exposures were calculated by facility, year and exposure categories. The exposure categories were based on grouping of all sampled jobs into eight categories with similar potential for exposure. An industrial hygiene-based regression model was used to estimate exposure to ethylene oxide for each exposure category. This model predicted exposures to ethylene oxide within 1.1 ppm (2.0 mg/m^3) of a validation data set (46 measurements not used in the model), with a standard deviation of 3.7 ppm (6.8 mg/m^3)

(Hornung *et al.*, 1994). Cumulative exposure for each individual was estimated by integration of estimated ppm ethylene oxide for each job held multiplied by the duration of time (days) spent in the job.

For the entire cohort, there was no increase in mortality from hematopoietic cancer. There was a slight but significant increase among men, however, but a decrease among women (Steenland *et al.*, 1991). The SMR for deaths due to "all haematopoietic neoplasms" among the group with the highest cumulative exposure was 124 (not statistically significant; 95% CI = 66–213), and the trend with cumulative exposure was not statistically significant. For the group with the highest cumulative exposure, the SMRs for non-Hodgkin's lymphoma and leukemia/aleukemia were 192 (95% CI = 77–395) and 75 (95% CI = 15–218), respectively. Increased mortality from kidney cancer (SMR = 322; 95% CI = 139–635) was observed in the mid-cumulative exposure group; however, no trend with exposure was observed (Stayner *et al.*, 1993).

When the results for "all haematopoietic neoplasms" were stratified according to sex, increased mortality (SMR = 196; 95% CI = 101–343) was observed among males in the highest exposure category, and there was a suggestive positive trend in the SMRs with exposure. When results for all workers were stratified according to time since first exposure, the greatest excess in deaths due to "haematopoietic neoplasms" was observed among workers with more than 20 years since their first exposure (SMR = 155; 95% CI = 77–277). Regression analysis revealed a highly statistically significant exposure–response relationship between cumulative exposure to ethylene oxide and mortality from lymphocytic leukemia and non-Hodgkin's lymphoma combined (termed "lymphoid" neoplasms and combined based on the consideration that these neoplasms may represent different expressions of the same underlying disease process). A marginal relationship was also observed between cumulative exposure and mortality from all hematopoietic neoplasms and from non-Hodgkin's lymphoma. There was a positive, but not statistically significant, exposure–response relationship between cumulative exposure and leukemia. Inclusion of a 5-year lag period yielded a stronger exposure–response relationship for "lymphoid" neoplasms; the relationship between cumulative exposure and mortality from all hematopoietic neoplasms and from non-Hodgkin's lymphoma was statistically significant, after inclusion of a 10-year lag period in the analysis. A negative exposure–response relationship was observed between cumulative exposure and cancers of the stomach, pancreas, brain and kidney (Stayner *et al.*, 1993).

While this is one of the few studies for which there are individual estimates of cumulative exposure, the monitoring data on which these estimates are based are limited to those collected after 1978 (however, results for the subgroup of this cohort exposed before 1978 were essentially identical to those for the entire cohort, suggesting that exposures may have been similar). Exposure to ethylene oxide was, however, relatively unconfounded by concomitant exposures to other substances, with none being identified. Although this is by far the largest of all of the studies conducted to date, the average follow-up period was short; 28% of workers had attained >20 years since first exposure (average duration of follow-up, 16 years; mean duration of exposure, 4.9 years). In this regard, it should be noted that five of the seven men who died of leukemia died in the most recent calendar period, generating statistically significant excess mortality for these years (SMR = 345; 95% CI = 111–806), and additional follow-up of this cohort is desirable. The variation in response between men and women in this study cannot be explained on the basis of sex ratio of the study population (i.e., small numbers of women); indeed, a greater proportion of the population was female (55% versus 45%).

In a subsequent analysis of data from the cohort evaluated by Steenland *et al.* (1991), in which the categorization of non-Hodgkin's lymphoma included an additional International Classification of Disease category that was omitted in the original Steenland *et al.* analysis (i.e., "other neoplasms of lymphoid tissue"), Wong and Trent (1993) reported increased mortality due to non-Hodgkin's lymphoma in males (SMR = 247; 95% CI = 141–402). No indication of an exposure–response relationship associated with either duration of employment or latency was observed. Similarly, there was no mortality pattern by latency or duration of employment for any cancer site examined. While this study is slightly larger than the corresponding study by Steenland *et al.* (1991), individual estimates of exposure frequency and intensity were not assigned.

Cancer risks were not significantly increased in a cohort of 2170 male and female Swedish workers exposed to ethylene oxide at two plants producing disposable medical equipment (Hagmar *et al.*, 1995). The risk of lymphopoietic/hematopoietic cancers was elevated (standardized incidence ratio [SIR] = 1.78; 95% CI = 0.65–3.88; 6 observed cases); two of the cases had leukemia (SIR = 2.44; 95% CI = 0.3–8.81). When the analysis excluded workers with cumulative exposures to ethylene oxide below the median value of 0.13 ppm-years, but included a minimum 10-year latency period, there was an increased (although not statistically significant) risk of leukemia (SIR = 7.14; 95% CI = 0.87–25.8; 2 observed cases). Cases with leukemia had a slightly higher cumulative exposure to ethylene oxide than the average cohort member. In this study, the levels of adducts in hemoglobin correlated well with the estimated exposure levels (Hagmar *et al.*, 1995). This is one of the only studies in which there were cumulative estimates of individual exposure; moreover, biological dosimetry of hemoglobin adducts was conducted to corroborate exposure estimates. Exposures were also mainly to ethylene oxide; the only other exposures were to methyl formate or fluorochlorocarbons. However, the mean duration of follow-up was relatively short (11.6 years), and exposure levels were relatively low for most workers, since fewer than 200 workers had more than 1 ppm-year of cumulative exposure.

A nested case–control study of 10 cases of Hodgkin's disease among male employees of a Belgian chemical manufacturing firm revealed a statistically significant increased risk associated with exposure to ethylene oxide (OR = 8.5; 95% CI = 1.4–39.9; 3 exposed cases) (Swaen *et al.*, 1996). The risk remained significantly elevated after restricting the analysis to individuals with durations of exposure of more than 10 years. The expected number of cases was 2.01 (SIR = 497; 95% CI = 238–915).

No statistically significant increased risks of cancer of the hematopoietic system or other sites were observed in a number of other epidemiological studies, in which there were no estimates of individual exposure and small numbers of hematopoietic and other cancers (Morgan *et al.*, 1981; Gardner *et al.*, 1989; Kiesselbach *et al.*, 1990; Olsen *et al.*, 1997). In the study by Kiesselbach *et al.* (1990), there were no increases in leukemias or total hematopoietic cancers, nor were there any trends associated with exposure intensity, duration of exposure or latency in 3658 men from six chemical companies, with median length of exposure of 9.6 years. Gardner *et al.* (1989) reported a small excess of leukemia mortality among chemical workers (3 observed/1.33 expected) and a deficit among hospital workers (0 observed/0.76 expected), although neither was statistically significant, in 2876 men and women from four companies that produced or used ethylene oxide and eight hospitals that used ethylene oxide sterilizers (average duration of follow-up not reported). Morgan *et al.* (1981) observed non-significant excesses of brain cancer, pancreatic cancer and Hodgkin's disease but a deficit of leukemia in 767 men at an ethylene oxide production plant. For the entire cohort examined by Olsen *et al.* (1997), there were non-statistically significant excess deaths from cancer of the large intestine, lung, kidney, lymphopoietic/hematopoietic tissue and other lymphatic tissues. Among those involved only in the production of ethylene chlorohydrin, the SMR was increased for lymphopoietic/hematopoietic cancer (SMR = 149; 95% CI = 60–307; 7 observed/4.7 expected).

In two additional small studies, significantly increased risks of lymphosarcoma/reticulosarcoma and breast cancer have been observed by Bisanti *et al.* (1993) and Norman *et al.* (1995), respectively. In the former investigation, the SMR for lymphosarcoma/reticulosarcoma was 682 (4 observed deaths, $p < 0.05$) among 1971 chemical workers licensed to handle ethylene oxide between 1938 and 1984 in Italy, in comparison with the local population (mean length of follow-up, 9.8 years; no estimates of individual exposure). However, there was no association with duration or latency, although the former could not be accurately determined.

A meta-analysis of results from 13 epidemiological studies published between 1979 and 1993 was conducted by Shore *et al.* (1993). The magnitude and the consistency (heterogeneity) of the relative risks were evaluated for the individual and combined studies, along with any trends associated with intensity or frequency of exposure, duration of exposure or time since first exposure (latency) for the cancers of greatest interest — namely, cancers of the pancreas, brain, stomach, leukemia and non-Hodgkin's lymphoma. For leukemia, SMRs from the individual studies were heterogeneous, due exclusively to the results reported by Hogstedt (1988). The summary SMR (sSMR) was 1.06 (95% CI = 0.73–1.48); when accounting for heterogeneity, the SMR was 1.06 (95% CI = 0.55–2.02) (Shore *et al.*, 1993). There was no consistency in the trends associated with the frequency and intensity of exposure for the individual studies, nor were any of the trends statistically significant. No trend with respect to frequency, intensity or duration of exposure was observed for the risk of leukemia for all studies combined; however, there was a suggestion that risks increased with the latency period. The sSMR for non-Hodgkin's lymphoma was not significantly increased (1.35; 95% CI = 0.93–1.90); the test for heterogeneity was not statistically significant. Although risks associated with the frequency or intensity of ethylene oxide exposure could be examined in only three studies, no trends were observed in either the individual or combined studies, although the positive trend by cumulative exposure in the largest study was noted. No trends with respect to duration of exposure or latency were noted. There was a lack of homogeneity among the relative risks for stomach cancer, due to the results of one study reported by Hogstedt (1988), in which the SMR was 7.1. The overall sSMR for stomach cancer for all of the studies, taking this heterogeneity into account, was 1.28 (95% CI = 0.73–2.26). No trends associated with the intensity or duration of exposure, latency or cumulative exposure were observed. The sSMRs for pancreatic cancer (0.98; 95% CI = 0.69–1.36), brain and nervous system cancer (0.89; 95% CI = 0.39–2.04, taking into account heterogeneity) and all cancers (0.94; 95% CI = 0.88–1.01) were not increased, nor were any trends observed (Shore *et al.*, 1993). No attempt was made to weight the studies according to quality, although there was a narrative critique of each. The authors also noted that data on exposure to ethylene oxide were inadequate in most of the studies, but that the cumulative exposure analysis by Stayner *et al.* (1993) represented a significant advance in the quantitative analysis of effects of ethylene oxide.

Teta *et al.* (1999) reported on an update of the Shore *et al.* (1993) meta-analysis, using methods and studies similar to those employed by Shore *et al.* (1993), but also including data from Hagmar *et al.* (1995) and Olsen *et al.* (1997). Similar to the findings reported by Shore *et al.* (1993), the meta-SMRs (mSMRs) for non-Hodgkin's lymphoma, leukemia, and cancer of the pancreas, brain and stomach were 1.34 (95% CI = 0.96–1.89), 1.08 (95% CI = 0.61–1.93), 0.95 (95% CI = 0.69–1.31), 0.96 (95% CI = 0.49–1.91) and 1.23 (95% CI = 0.71–2.13), respectively. Reportedly, there were no statistically significant trends with respect to duration or intensity of exposure (data not shown). There was a reportedly statistically significant ($p < 0.05$) trend with respect to latency and brain cancer, based on four studies (data not shown).

3.0 PROPOSED ASSESSMENT OF "TOXIC" UNDER CEPA

3.1 CEPA 11(a): Environment

The environmental risk assessment of a PSL substance is based on the procedures outlined in Environment Canada (1997a). Analysis of exposure pathways and subsequent identification of sensitive receptors are the basis for selection of environmental assessment endpoints (e.g., adverse reproductive effects on sensitive fish species in a community). For each endpoint, a conservative Estimated Exposure Value (EEV) is selected and an Estimated No-Effects Value (ENEV) is determined by dividing a Critical Toxicity Value (CTV) by an application factor. A hyperconservative or conservative quotient (EEV/ENEV) is calculated for each of the assessment endpoints in order to determine whether there is potential ecological risk in Canada. If these quotients are less than one, it can be concluded that the substance poses no significant risk to the environment, and the risk assessment is completed. If, however, the quotient is greater than one for a particular assessment endpoint, then the risk assessment for that endpoint proceeds to an analysis where more realistic assumptions are used and the probability and magnitude of effects are considered. This latter approach involves a more thorough consideration of sources of variability and uncertainty in the risk analysis.

3.1.1 Assessment endpoints

All reported Canadian releases of ethylene oxide are to air, and pathways analysis indicates that following release to air, ethylene oxide is unlikely to partition to other compartments in significant amounts. Once in the atmosphere, ethylene oxide is not expected to contribute to ground-level ozone or climate change, nor will it deplete the ozone layer. Its atmospheric half-life may range from 38 to 382 days. Its high water solubility may encourage some washout via precipitation; however, available evidence indicates that this removal mechanism has minimal impact.

Although releases to water and soil are not common, it is understood that some releases to these media may occur in the event of a spill or similar release scenario. Persistence in these media is not expected, as ethylene oxide has a high Henry's law constant (12.2–19.9 Pa·m^3/mol), and the experimental data indicate that volatilization will occur rapidly from water ($t_{½}$ ~1 hour). Although no information was available regarding concentrations of ethylene oxide in wastewater discharged from Canadian manufacturing and processing operations, releases from these sources are expected to be minimal, especially when one considers temperatures and retention times in wastewater treatment processes. Based on these considerations, aquatic concentrations are expected to be negligible; therefore, adverse effects on aquatic organisms are also considered negligible.

Given that the primary medium of release for ethylene oxide is the atmosphere and that the chemical's properties cause it to remain in and react in that compartment, the assessment endpoint for determination of toxicity under CEPA Paragraph 11(a) will be for atmospherically exposed organisms. One of the more significant effects that has been observed following atmospheric exposure is the induction of genetic mutations in microorganisms, plants and animals. Other effects observed in laboratory animals include carcinogenicity, reduced kidney and adrenal weights, and increased incidence of inflammatory lesions in the lungs, nasal cavity, trachea and internal ear, as well as decreases in weight, changes in posture, demyelination of parts of nervous tissue, decreased sperm count and induction of other adverse reproductive effects. Although evidence is strong concerning ethylene oxide-induced genotoxic and carcinogenic effects (see Sections 2.4.4.1 and 2.4.4.2), the actual population-level impact to wildlife from these endpoints is not completely clear when one considers population resilience, dose–response and induction frequency. Among the observed effects, adverse impacts on reproduction are decidedly the endpoint that would have the greatest potential to adversely impact wildlife population levels. Other effects may occur at slightly lower concentrations.

3.1.2 Environmental risk characterization

3.1.2.1 Terrestrial biota

There are only a few ambient measurements of ethylene oxide in Canada. Some limited additional data were identified for the urban area of Los Angeles, California (Havlicek *et al.*, 1992). The ambient air concentrations from Los Angeles are likely to be higher than would be expected to occur in most Canadian situations. Los Angeles is located in a geographic area (i.e., a basin) that can cause reduced air movement and contribute to higher pollutant levels in the air. For a hyperconservative scenario, it will be assumed that the concentrations of ethylene oxide in Los Angeles are comparable to maximum concentrations that may be found in Canada. The maximum mean 24-hour ambient air concentration detected in the Los Angeles urban area was found to be 956 $\mu g/m^3$ (95% confidence limit [CL] = 0.75–5600 $\mu g/m^3$; n = 6) in May 1990 and will be used as the EEV to represent a worst-case Canadian atmospheric concentration.

The EEV for ethylene oxide is therefore 956 $\mu g/m^3$.

Toxicity data are very limited for all of the environmental compartments. The most sensitive terrestrial organisms were found to be laboratory test rodents, which will be considered as surrogates for Canadian wild rodent species. The CTV is derived from a reproductive study by Snellings *et al.* (1982b); the effects reported in this study were determined to represent the most significant ecological endpoint in terms of the potential to adversely impact natural wildlife populations. Snellings *et al.* (1982b) exposed 3- to 4-week-old Fischer 344 rats to ethylene oxide vapour at 10, 33 and 100 ppm (18.3, 60.4 and 183 mg/m^3) for 6 hours per day, 5 days per week, then exposed only females at the same rate from day 0 to day 19 of gestation, 7 days per week. The authors reported that at the highest exposure concentration (183 mg/m^3), there was a significant drop in the number of pups born per litter. There were also fewer implantation sites and fewer pups born per implantation site.

The CTV for terrestrial animals is 183 mg/m^3 from the rat study of Snellings *et al.* (1982b). To derive the ENEV from this study, a suitable application factor is used. The magnitude of the application factor takes into consideration the fact that the CTV is based on a relatively small data set and was the maximum concentration tested in the study. In addition, the study was conducted in the laboratory (not the field), and no statistics were applied to determine whether 183 mg/m^3 is truly the lowest adverse effect concentration, nor was the study designed to make this determination. For these reasons, and because effects less clearly related to population-level impacts (e.g., decreased weight) were observed at slightly lower levels, a relatively large application factor of 100 is applied to the CTV, as outlined in Environment Canada (1997a), to determine the ENEV.

The ENEV for terrestrial biota is therefore 1830 μg/m^3.

The hyperconservative quotient is calculated by dividing the EEV of 956 μg/m^3 by the ENEV of 1830 μg/m^3.

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{956\ \mu g/m^3}{1830\ \mu g/m^3}$$

$$= 0.52$$

Since the hyperconservative quotient is less than one, the risks posed by chronic exposure of terrestrial biota to ethylene oxide in the Canadian environment are expected to be minimal.

3.1.2.2 Discussion of uncertainty

There are a number of sources of uncertainty in this environmental risk assessment. The primary source is the lack of Canadian ambient environmental concentration data. Measured atmospheric concentrations reported in the assessment are from California and a small number of Canadian locations. The use of measured ambient air concentrations is preferred to the use of modelled results, and although the EEV chosen is more than an order of magnitude higher than concentrations predicted near Canadian sources based on modelling studies, it represents a conservative estimate of a potential concentration in the Canadian atmosphere.

No ambient measurements of ethylene oxide in water, soil, sediment or groundwater in Canada were located during the literature search. This is due to a number of factors, including the lack of monitoring programs designed to measure ethylene oxide as well as the physical/chemical properties of ethylene oxide, which govern its fate and behaviour, resulting in limited entry into or rapid removal from environmental compartments other than air.

An additional source of uncertainty is the limited number of toxicity data for species in all environmental compartments. Ideally, there should be enough toxicity data to represent a wide variety of species in each environmental compartment. For example, freshwater fish are represented by fathead minnow and goldfish, but no other species. Similarly, only one freshwater aquatic invertebrate and one marine invertebrate are represented in the toxicity database. However, based on the atmosphere being the predominant compartment of environmental release, and considering the environmental fate and behaviour of ethylene oxide, the limitations in the toxicity data were considered admissible.

Similar limitations are associated with the data available on effects on terrestrial organisms. In addition, although mutagenic effects have been observed in a variety of terrestrial plants and mammals, their population-level impacts are uncertain. To account for these uncertainties, a relatively large application factor was used in the risk analysis to derive an ENEV.

Despite a few data gaps regarding the environmental concentrations and effects of ethylene oxide, the data available at this time are considered adequate for drawing a conclusion on the environmental risk of ethylene oxide in Canada.

3.2 CEPA 11(b): Environment upon which human life depends

The theoretical atmospheric lifetime of ethylene oxide is long enough to allow a small percentage of the amount emitted to reach the stratosphere; however, ethylene oxide does not degrade to an active intermediate and therefore does not induce the depletion of the ozone layer. Its POCP is considered insignificant, and its GWP is considered minimal.

3.3 CEPA 11(c): Human health

3.3.1 Estimated population exposure

Information on monitored levels of ethylene oxide in air, drinking water and foodstuffs in Canada is exceedingly limited, being restricted to detection in a few samples of ambient and indoor air in a small monitoring survey.

Although available data are limited, deterministic estimates of total daily intakes of ethylene oxide for the general population in Canada were developed — primarily to compare relative contributions from various media — on the basis of the limited monitoring data in ambient and indoor air (Conor Pacific Environmental, 1998), a limited survey of levels in foodstuffs in Denmark (Jensen, 1988) and concentrations in drinking water and air predicted by the ChemCAN 4 regional fugacity model, when advective input from bordering U.S. states was included (Health Canada, 1999a). Based on this approach, estimated intakes (expressed as µg/kg-bw per day) of ethylene oxide from food exceeded those from air; however, the extent of the uncertainties associated with the estimates, particularly in foodstuffs (i.e., based on measured levels in a limited number of food products consumed in other countries, and incorporating highly conservative and uncertain estimates for the consumption of selected food products [i.e., spices]), precludes any degree of confidence in these conclusions.

Owing to these limitations, the focus of the remainder of this section and the basis for risk characterization is exposure in air. This approach is supported on the basis that all releases from point sources controllable under CEPA are to air, that ethylene oxide is generally transferred to air following release to other media and that it is not expected to accumulate in sediment or soil or bioaccumulate, as a result of its high water solubility and vapour pressure.

The concentration of ethylene oxide predicted for ambient air (i.e., 6.2×10^{-3} µg/m^3) by ChemCAN fugacity modelling was considered the basis for the minimum estimate of exposure via inhalation. Censored mean concentrations of ethylene oxide in outdoor and indoor air (i.e., 0.34 µg/m^3 and 0.17 µg/m^3, respectively), derived from the multimedia exposure study, were considered to represent the maximum concentrations to which the general population is exposed daily indoors and outdoors, respectively. Upper-bounding estimates of exposure via inhalation for the general population in Canada were based upon the maximum concentrations of ethylene oxide in outdoor and indoor air (i.e., 4.9 µg/m^3 and 4.0 µg/m^3, respectively) reported from the multimedia exposure study (Conor Pacific Environmental, 1998). Mean concentrations in ambient air sampled in Los Angeles, California, ranged from 0.038 to 955.7 µg/m^3 (Havlicek *et al.*, 1992)

Exposure to ethylene oxide in ambient air may be substantially higher for populations residing in the vicinity of point sources. A concentration of 2 µg ethylene oxide/m^3 was predicted for outdoor air in close proximity to hospitals in Canada (Environment Canada, 1999) and Florida (Tutt and Tilley, 1993). A concentration of 11 µg ethylene oxide/m^3 was predicted for outdoor air in close proximity to a sterilization facility in Florida (Tutt and Tilley, 1993). A maximum 1-hour concentration of 20.1 µg ethylene oxide/m^3 was predicted for outdoor air near a production facility for ethylene glycol in Alberta (Environment Canada, 1997b).

Limitations of the data preclude development of meaningful probabilistic estimates of exposure of the general population to ethylene oxide in air.

3.3.2 Hazard characterization

Owing to the physical/chemical properties of ethylene oxide, most toxicological studies have involved inhalation, which is the principal route of exposure of the general population in the vicinity of sources. There have been only a few investigations of potential health effects associated with the ingestion of this substance.

Pathways for the metabolism of ethylene oxide and subsequent elimination of its metabolites involve either hydrolysis or enzymatic conjugation with glutathione catalyzed by the GSTT1 enzyme. The parent compound is the putative toxin, interacting directly with DNA and proteins. Data from laboratory animals are consistent, in part, with glutathione conjugation being a detoxification pathway, with interspecies variations in toxicity correlating with greater specific activity of cytosolic GSTT1 in smaller species (i.e., mice versus rats). Available data indicate that the metabolism of ethylene oxide in humans and laboratory animals is qualitatively similar, although there may be quantitative variations, since conversion through hydrolysis appears to predominate in larger species (such as dogs). A genetic polymorphism in the expression of the GSTT1 enzyme in humans contributes to potential for considerable intraspecies (interindividual) variation in metabolism and, hence, response to ethylene oxide, which has been confirmed in *in* *vitro* studies, although the relative importance of this pathway in the detoxification of ethylene oxide in humans is unknown.

3.3.2.1 Carcinogenicity

Information relevant to assessment of the carcinogenicity of ethylene oxide has been derived from epidemiological studies of occupationally exposed workers, carcinogenesis bioassays in laboratory animals, as well as supporting data related to genotoxicity and metabolism.

While increases in mortality due to liver, colon, breast, bladder, kidney, esophageal, stomach, brain or pancreatic cancer have occasionally been reported in epidemiological studies of workers exposed to ethylene oxide, evidence is not consistent or convincing.

However, within the limits of sensitivity of identified studies, available epidemiological evidence for an association between exposure to ethylene oxide and lymphopoietic/hematopoietic cancer is suggestive, although inconclusive, based on consideration of traditional criteria for causality, as outlined below (e.g., consistency, specificity, dose–response relationship and biological plausibility).

Although not reported in all studies and generally based on small numbers of observed cases, increased risks of leukemia, all hematopoietic neoplasms (or non-Hodgkin's lymphoma in the same cohort), lymphopoietic/hematopoietic cancers or lymphosarcoma/reticulosarcoma have been reported for production and sterilization workers (Hogstedt, 1988), workers in plants producing sterilized medical supplies and spices (Steenland *et al.*, 1991; Stayner *et al.*, 1993; Wong and Trent, 1993) and those producing disposable medical equipment (Hagmar *et al.*, 1995), respectively (Table 5). It is of interest that these excesses occurred in workers exposed primarily to ethylene oxide in the sterilization of medical supplies and equipment rather than in facilities associated with its production and/or use, where numerous other substances would have been present.

Risks for lymphopoietic/hematopoietic cancers among the various industrial cohorts have varied, although in general by less than 2-fold. For example, in meta-analyses, while the risk for leukemia was not significantly increased (sSMR = 1.06; 95% CI = 0.73–1.48 or 0.55–2.02, corrected for heterogeneity), the sSMR for non-Hodgkin's lymphoma was suggestively although not significantly increased (1.35; 95% CI = 0.93–1.90) (Shore *et al.*, 1993). However, it should be noted that with the single exception of the investigation of workers at ethylene production plants in which there was no increase in hematopoietic cancers reported (Teta *et al.*, 1993), length of follow-up was relatively short in the critical investigations, averaging 11.6 years and 16 years for the more reliable studies in which excesses were observed — namely, Hagmar *et al.* (1995) and Steenland *et al.* (1991). In the largest investigation (Steenland *et al.*, 1991; Stayner *et al.*, 1993), only 28% of workers had attained greater than 20 years since first exposure, and five of the seven men who died of leukemia did so within the most recent calendar period. Limited strength of the observed associations could be due, therefore, at least in part, to the limited period of follow-up.

In meta-analysis, although risks associated with the frequency or intensity of ethylene oxide exposure could be examined in only three studies, no trends were observed in either the individual or combined studies, although the positive trend by cumulative exposure in the largest investigation was noted (Shore *et al.*, 1993). There were no trends in the individual or combined studies with respect to duration of exposure or latency. However, in the largest cohort examined (more than 18 000 workers who had been exposed primarily to ethylene oxide) with the most extensive characterization of individual exposure and the only investigation in which cumulative exposure was quantitatively estimated, regression analysis revealed a highly significant ($p < 0.01$) exposure–response relationship between cumulative exposure to ethylene oxide and mortality due to lymphocytic leukemia and non-Hodgkin's lymphoma combined (termed "lymphoid" neoplasms) (Steenland *et al.*, 1991; Stayner *et al.*, 1993). An association was also observed between cumulative exposure to ethylene oxide and mortality from all hematopoietic neoplasms and non-Hodgkin's lymphoma; the exposure–response relationship between cumulative exposure and leukemia was positive, although not statistically significant. Of interest is the additional observation that none of the other measures of exposure (i.e., duration, average and maximum) in this analysis were predictors of hematopoietic cancers, consistent with results of other investigations. Difficult to explain, though, in the context of causality is the decrease in hematopoietic cancer in women versus the increase in men observed in this cohort.

Therefore, the available epidemiological studies of the association between hematological cancers and exposure to ethylene oxide in occupationally exposed human populations fulfil, in part only, some of the traditional criteria for causality, including exposure–response and temporal relationship. Strength of the association is weak, although this may be a function of inadequate length of follow-up in existing studies. The observation of variations in response among males and females in the largest cohort study with the most extensive exposure analyses begs, to some extent, coherence.

Clearly, therefore, epidemiological evidence for the association between exposure to ethylene oxide and hematological cancers is not convincing in its own right. Assessment of the weight of evidence for carcinogenicity in human populations should not, however, be considered in isolation from the extensive supporting data on carcinogenicity, genotoxicity and inter- and intraspecies variations in metabolism and response.

Cytogenetic changes (i.e., increased frequency of chromosomal aberrations, micronuclei or sister chromatid exchange) within the peripheral blood cells have been reported in a number of cross-sectional studies, principally of populations exposed occupationally to ethylene oxide (Table 4). None of these studies is convincing in its own right, and inherent limitations of cross-sectional investigations make them less reliable than cohort or case–control studies as a basis for inference of causality. Nevertheless, observation of cytogenetic effects in some groups of workers exposed to elevated concentrations of ethylene oxide in the most sensitive studies, while not necessarily an indicator of chronic adverse health outcomes, provides some limited additional supporting evidence for the ability of ethylene oxide to interact with the genome in individuals exposed to this substance. Indeed, in comparison with that for other substances, the relative consistency of the data across studies is rather striking, although there are some inconsistent observations within studies, particularly in relation to the nature of clastogenic effects observed at various time points and exposures. For example, while not well characterized in individual studies, the increased occurrence of cytogenetic changes has tended to be observed at exposures to ∃5 ppm (9.2 mg/m^3) ethylene oxide, thereby satisfying the criterion of exposure–response. In addition, while the numbers of subjects were relatively small in some of the investigations, results were consistently positive in the more sensitive (i.e., larger) studies of populations exposed to higher concentrations (i.e., those with >25 subjects, such as at site III in Galloway *et al.* [1986] and Stolley *et al.* [1984], high-dose group in Mayer *et al.* [1991], Ribeiro *et al.* [1994] and Richmond *et al.* [1985]). While there was inadequate control for confounding in several of the particularly small, early investigations (Garry *et al.*, 1979; Yager *et al.*, 1983), frequencies of clastogenic effects were sufficiently elevated in some cases that they were unlikely to be due to potential confounders (Laurent, 1988). It should also be noted that there was no information on genotype with respect to GSTT1 for the populations examined in these studies.

There is also overwhelming evidence for the biological plausibility of the carcinogenicity of ethylene oxide in human populations based upon data from carcinogenesis bioassays and other laboratory studies. An increased incidence of leukemias (although mononuclear) in F344 rats and lymphomas in mice (in addition to other types of tumours in both species) has been observed following inhalation of ethylene oxide (Lynch *et al.*, 1984a,b; Snellings *et al.*, 1984b; Garman *et al.*, 1985; Garman and Snellings, 1986; NTP, 1987). Available data are insufficient to support a plausible mode of induction of tumours, however. While the spectrum of tumours induced in rats and mice is consistent (in part) with variations between species and tissues in the detoxification of the compound by the GSTT1 pathway, there is no correlation with identified putatively responsible DNA adducts. However, the genotoxicity of ethylene oxide undoubtedly plays a critical role in tumour induction. Ethylene oxide is a potent alkylating agent that has been genotoxic in almost all available studies in laboratory animals. Gene mutations, DNA damage and cytogenetic effects have been observed routinely in bacterial, rodent and human cells exposed *in vitro* to ethylene oxide and in the somatic cells of laboratory species exposed *in vivo* to this substance.

Therefore, there is suggestive but inconclusive evidence (possibly attributable to the limitations of the studies) for an association between exposure to ethylene oxide and hematological cancers in occupationally exposed populations. There is rather consistent evidence that ethylene oxide interacts with the genome of cells within the circulatory system in occupationally exposed humans and overwhelming supporting evidence of biological plausibility based on carcinogenicity and genotoxicity in laboratory animals. Based on these considerations and the lack of qualitative differences in metabolism between humans and laboratory animals, ethylene oxide is considered highly likely to be carcinogenic to humans.

3.3.2.2 Heritable mutations

Although relevant data in humans are not available, dominant lethal mutations, heritable translocations, chromosomal aberrations, DNA damage and adduct formation in rodent sperm cells have been observed in a number of studies involving the exposure of rats and mice to ethylene oxide. Based upon the likely role for DNA alkylation in production of the genotoxic effects in germ cells in laboratory animals exposed to ethylene oxide, as well as the lack of qualitative differences in the metabolism of this substance between humans and animals (including DNA adduct formation), ethylene oxide can be considered a likely human germ cell genotoxicant.

3.3.2.3 Other non-neoplastic effects

3.3.2.3.1 Effects in humans

In humans, ethylene oxide vapour is irritating to the eyes, nose and throat. Aqueous solutions of ethylene oxide can be irritating to the skin, and, in some individuals, dermal irritation was associated with contact with ethylene oxide-sterilized materials and clothing. Ethylene oxide is considered an effective sensitizing agent (Bommer and Ritz, 1987; Bousquet and Michel, 1991). Type I (anaphylaxis) and Type IV (contact dermatitis) hypersensitivity reactions have been observed in individuals exposed to ethylene oxide. Anaphylactic reactions (ranging from mild to severe) have been noted among patients undergoing various forms of dialysis involving equipment sterilized by exposure to ethylene oxide. Asthmatic reactions may occur either alone or in combination with anaphylactic events, and case reports of occupational asthma attributed to ethylene oxide exposure have appeared (Dugue *et al.*, 1991; Verraes and Michel, 1995).

Neurological effects (including neurophysiological, neurobehavioural and histopathological effects) have been clearly documented in workers exposed to relatively high concentrations of ethylene oxide. These include effects related to sensorimotor polyneuropathy, cognition, language and speech disturbances and seizures. Other effects attributed to ethylene oxide have included numbness and weakness in the extremities, slow and clumsy alternating hand movements, decreased muscle stretch reflexes in extremities, heel-shin ataxia, unsteady and wide-based gait, reduced ankle reflexes, diminished or impaired psychomotor skills and reduced peripheral nerve conduction velocity. Amelioration of symptoms following the cessation of exposure has been commonly observed. In individuals exposed to >700 ppm (1281 mg/m^3) ethylene oxide, sural nerve biopsies revealed axonal degeneration with mild changes in the myelin sheath; muscle biopsies revealed degeneration atrophy (Kuzuhara *et al.*, 1983).

Evidence from epidemiological studies of reproductive effects of ethylene oxide in humans is considered to be limited, at best, with suggestive but inconclusive evidence, at present, of increased risks of spontaneous abortion in female hospital workers (Hemminki *et al.*, 1982, 1983) and dental assistants (Rowland *et al.*, 1996) exposed to ethylene oxide in sterilization of equipment. There is also a single report of increased risk of spontaneous abortion in one investigation of women with partners who had had some potential for exposure to this substance (Lindbolm *et al.*, 1991). While there are some consistent results in this regard, the available data are too limited to address other traditional criteria for causality such as strength and dose–response. With respect to biological plausibility, the data are supported, at least to some extent, by studies in animals that indicate that, among non-neoplastic effects, reproductive effects occur at lowest concentration.

Hematological changes (e.g., hematocrit, hemoglobin, lymphocytes, neutrophils) among workers occupationally exposed to higher concentrations of ethylene oxide have also been reported in some studies (Deschamps *et al.*, 1990; Schulte *et al.*, 1995). An increased prevalence of cataracts was noted among a small number of French hospital workers exposed to ethylene oxide (Deschamps *et al.*, 1990).

3.3.2.3.2 Effects in laboratory animals

In laboratory animals, ethylene oxide is moderately acutely toxic. Data on the non-neoplastic effects following repeated exposure are somewhat limited due to emphasis in past studies on the carcinogenicity of the compound. However, in available studies, ethylene oxide has induced a wide range of effects in laboratory animals, including those at the site of contact and those on the hematological, reproductive and neurological systems. Effects on the neurological and reproductive systems occur at lowest concentrations.

With respect to neurological effects, histological alterations in the axons within the nucleus gracilis of the medulla oblongata and demyelination of the distal portion of the fasciculus gracilis within the medulla of monkeys following long-term exposure (Sprinz *et al.*, 1982; Lynch *et al.*, 1984b) and abnormal gait and reduced locomotor activity in mice after subchronic exposure (Snellings *et al.*, 1984a) have been observed at lowest concentration. At higher concentrations, there is a wide range of more severe effects in rats, including awkward or ataxic gait, reversible paralysis and atrophy of the muscles of the hind limbs, accompanied, in some cases, by pathological evidence of axonal degeneration of myelinated fibres in nerves of the hind legs.

Reproductive effects in males observed in repeated-dose studies have included alterations in sperm morphology in rats (Mori *et al.*, 1991), changes in sperm count and motility in monkeys at lower concentrations and degeneration of the seminiferous tubules and reductions in epididymal and testicular weights in rats at higher concentrations. In reproductive studies, reductions in litter size and increased post-implantation losses in rats are observed at lowest concentrations.

Ethylene oxide is fetotoxic in the presence and absence of maternal toxicity at concentrations higher than those associated with adverse reproductive and neurological effects, but it is teratogenic only at very high concentrations.

3.3.3 Exposure–response analysis

Inhalation is the principal route of exposure of the general population to ethylene oxide in the vicinity of industrial sources (i.e., those controllable under CEPA). Moreover, virtually all of the available toxicological and epidemiological data relate to effects following exposure via this route. Indeed, information on exposure–response for ingestion of ethylene oxide is limited to reports from two (including one very early) studies in rats, in which gastric irritation and liver damage or histopathological changes in the stomach were observed in animals administered 100 mg ethylene oxide/kg-bw, 5 times per week for a total of 15 doses in 21 days (Hollingsworth *et al.*, 1956), or 7.5 mg ethylene oxide/kg-bw twice weekly for 150 weeks (Dunkelberg, 1982), respectively. The remainder of this section, therefore, addresses exposure–response for the inhalation of ethylene oxide.

While the metabolism of ethylene oxide appears to be qualitatively similar in humans and animals, quantitative variations have not been well characterized. Two physiologically based pharmacokinetic (PBPK) models for ethylene oxide have been developed and verified for the rat (Hattis, 1987; Krishnan *et al.*, 1992), although they have not been scaled to humans. Although subsequent studies have provided data that will ultimately be used in more refined PBPK models (Brown *et al.*, 1996), published reports of an updated model (including those for other species) have not been identified.

The parent compound is the putatively toxic entity, and exposures of the same concentration and duration are expected to result in equivalent toxicity across species. This is supported by the observed similarity in response to identical levels of exposure in the carcinogenicity bioassays in rats and mice. Therefore, no interspecies scaling to account for variations between inhalation rate to body weight ratios or body surface areas of humans to animals have been incorporated in the measures of dose–response reported here.

3.3.3.1 Carcinogenicity

Cancer is considered the critical endpoint for quantitation of exposure–response for risk characterization for ethylene oxide.[4] This is based on the observation that tumours (and somatic mutations) are the effects that occur at lowest concentration. A statistically significant increased incidence of brain tumours was observed at concentrations as low as 60.4 mg/m^3 in rats; moreover, incidences of several types of tumours were increased, although not significantly, at 18.3 mg/m^3. Moreover, the genotoxicity of ethylene oxide, for which the weight of evidence is consistent and convincing, undoubtedly plays a critical role in tumour induction.

Quantitation of exposure–response for cancer for ethylene oxide is based on studies in laboratory animals, since limitations of the existing epidemiological data prevent adequate consideration of traditional criteria for causality (particularly with respect to periods of follow-up in the largest investigations). Moreover, available data indicate that the metabolism and mode of action of ethylene oxide in humans and laboratory animals do not differ qualitatively.

Data suitable for analysis of exposure–response are available from two carcinogenesis bioassays in F344 rats (Lynch *et al*, 1984a,b; Snellings *et al.*, 1984b; Garman *et al.*, 1985; Garman and Snellings, 1986) and one in B6C3F$_1$ mice (NTP, 1987). In F344 rats, there were dose-related increases in the incidence of mononuclear leukemias, peritoneal mesotheliomas and brain tumours; in mice, the incidence of lung carcinomas, malignant lymphomas, uterine adenocarcinomas, mammary carcinomas and adenosquamous carcinomas and Harderian cystadenomas was increased.

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[4] However, in situations of short-term or intermittent exposure, other effects could be considered as critical.

Concentrations of ethylene oxide causing a 5% increase in tumour incidence over background (i.e., Tumorigenic Concentration$_{05}$s, or TC$_{05}$s) were calculated by first fitting the multistage model to the dose–response data (see Figure 2). The multistage model is given by:

$$P(d) = 1 - e^{-q_0 - q_1 d - \ldots - q_k d^k}$$

where d is dose, k is the number of dose groups in the study minus one, $P(d)$ is the probability of the animal developing a tumour at dose d and $q_i > 0$, $i = 1,\ldots, k$ are parameters to be estimated.

The models were fit using GLOBAL82 (Howe and Crump, 1982), and the TC$_{05}$s were calculated as the concentration C that satisfies:

$$\frac{P(C) - P(0)}{1 - P(0)} = 0.05$$

A chi-square lack of fitness test was performed for each of the three model fits. The degrees of freedom for this test are equal to k minus the number of q_i's for which estimates are non-zero. A p-value less than 0.05 indicates a significant lack of fit.

The TC$_{05}$s and the corresponding 95% lower confidence limit (95% LCL) were adjusted for continuous exposure by multiplying the values by either 7/24 × 5/7 (for the study reported by Lynch *et al.* [1984a,b], in which animals were exposed for 7 hours per day, 5 days per week) or 6/24 × 5/7 (for the studies reported by Snellings *et al.* [1984b], Garman *et al.* [1985], Garman and Snellings [1986] and NTP [1987], in which animals were exposed for 6 hours per day, 5 days per week). Model parameters, the adjusted TC$_{05}$s and corresponding 95% LCLs are presented in Table 6.

For the tumours in rats, characterization of exposure–response was optimal in the study reported by Snellings *et al.* (1984b), Garman *et al.* (1985) and Garman and Snellings (1986). The number of dose groups was greatest in this bioassay, and two of the three doses were in a lower concentration range than in the study by Lynch *et al.* (1984a,b) (0, 18.3, 60.4 or 183 mg/m^3 versus 0, 92 or 183 mg/m^3). Dose spacing was excellent (approximately 3-fold variation between concentrations), both sexes were exposed and group sizes were slightly larger (120 per sex per group) than in the bioassay of Lynch *et al.* (1984a,b) (80 males per group).

For the study in rats in which exposure–response was best characterized (Snellings *et al.*, 1984b; Garman *et al.*, 1985; Garman and Snellings, 1986), the TC$_{05}$s range from 2.2 mg/m^3 (95% LCL = 1.5 mg/m^3) for mononuclear leukemia[5] in F344 rats to 31.0 mg/m^3 (95% LCL = 16.1 mg/m^3) for brain tumours. TC$_{05}$s for comparable tumours in the study in which exposure–

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[5] Mononuclear cell leukemias are unique to the F344 strain of rat. These tumours arise spontaneously, primarily in older animals. The exact etiology of this tumour type, including cell of origin, has not been definitively identified.

response was less well characterized (Lynch *et al.*, 1984a,b) were somewhat higher (12.5–31.9 mg/m^3, respectively).

Values of the TC_{05}s in mice ranged from 6.7 mg/m^3 (95% LCL = 4.2 mg/m^3) for Harderian cystadenomas in males to 22.7 mg/m^3 (95% LCL = 11.4 mg/m^3) for uterine adenocarcinomas. It should be noted, however, that characterization of exposure–response in the NTP (1987) bioassay on which these values are based was not optimal; there were only two dose groups and controls, with the lowest administered concentration being 92 mg/m^3.

For none of the modelled TC_{05}s was there significant lack of fit ($p > 0.05$, Table 6). For the study in rats in which exposure–response was best characterized (Snellings *et al.*, 1984b; Garman *et al.*, 1985; Garman and Snellings, 1986) and that in mice (NTP, 1987), fits for malignant lymphomas and mammary adenocarcinomas and adenosquamous carcinomas (combined) in females in the latter investigation were poorest ($p = 0.06$ and 0.08, respectively).

Based on modelling (using THC program; Howe, 1995) of the incidence of *Hprt* mutations in splenic T-lymphocytes of male $B6C3F_1$ mice (Big Blue®, *lacI* transgenic) exposed to ethylene oxide for 4 weeks[6] (Walker *et al.*, 1997a), the Benchmark $Concentration_{05}$ (BMC_{05}) for somatic cell mutations (i.e., the concentration associated with a 5% increase in the incidence of *Hprt* mutation) (adjusted for intermittent to continuous exposure) was within the range of the lowest TC_{05}s in rats and mice. It should be noted, however, that characterization of exposure–response in Walker *et al.* (1997a) was not optimal; although there were three dose groups and controls, the lowest administered concentration was 92 mg/m^3.

In the interest of utilizing all available data to inform characterization of exposure–response, the tumorigenic potencies developed based on studies in animals were compared with risks of hematological cancers reported in epidemiological studies in populations occupationally exposed to ethylene oxide. The protocol and results of these analyses are reported elsewhere (Health Canada, 1999b). Results indicated that risks predicted based on the most sensitive outcome in rats (mononuclear cell leukemia in female F344 rats) were consistent with the confidence intervals of the SMRs observed for both leukemias overall and all hematopoietic neoplasms in males in the cohort study by Stayner *et al.* (1993) (i.e., the only epidemiological study in which individual cumulative exposure was characterized). However, the limitations of this comparative exercise preclude its meaningful contribution to quantitation of risk. These include uncertainties of the available epidemiological data on ethylene oxide, which prevent adequate consideration of traditional criteria for causality (particularly with respect to periods of follow-up in investigations of greatest sensitivity). Moreover, meaningful direct comparison of potency in laboratory animals with that in humans is precarious at best, in light of the inadequacy of available information on interspecies variations in kinetics and metabolism and mode of action to serve as a basis for characterization of site concordance between animals and humans and the extremely wide range of the confidence limits on the SMRs in the epidemiological studies.

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[6] The mean frequency ($\times 10^{-6}$) of *Hprt* mutations was 2.2, 3.8, 6.8 and 14.1 in animals exposed to 0, 92, 183 or 366 mg/m^3, respectively.

3.3.3.2 Heritable mutations

There have been several efforts to quantify the genetic risk to the offspring of humans exposed to ethylene oxide, the most comprehensive of which is that of Natarajan *et al.* (1995), which documents the outcome of deliberations of an international workshop of experts. This exercise was undertaken to identify data gaps that would permit a more refined estimate of heritable genetic risk from ethylene oxide and to acquire experience with the parallelogram approach to better inform future efforts in this area. The outcome is presented here primarily as a basis for comparison with the tumorigenic potencies for cancer, to ensure that measures developed for this endpoint will be protective for other reported effects. However, it meets this objective only in part, since the calculated genetic risk is underestimated, is based on induced dominant visible mutations only and does not take into consideration recessive mutation, dominant lethal mutations or heritable translocations. The relevant data for these endpoints were judged either not to be sufficiently robust or to result in a very small increment in actual genetic risk to live offspring. An increase in dominant lethal mutations in humans might be manifested in an increase in spontaneous abortions, as reported in some hospital sterilization workers (Hemminki *et al.*, 1982).

The analysis was based on induced dominant visible mutations in mice from a study by Lewis *et al.* (1986), which was designed to mimic human occupational exposure (i.e., involving exposure for prolonged periods in order to cover all stages of spermatogenesis). Using the parallelogram approach and additional quantitative data on somatic mutations (*Hprt* in splenocytes) in mice (Walker *et al.*, 1994) and in an occupationally exposed human population (*HPRT*) (Tates *et al.*, 1991), it was estimated that exposure for one working year (1800 hours) to 1 ppm ethylene oxide would lead to an incremental risk of 4×10^{-4} above background that a disease with dominant inheritance would be transferred to the offspring. As a basis for comparison with the potency estimates for cancer, the BMC_{05} for this effect would be 46 mg/m^3.[7]

Identified sources of uncertainty of the estimate were the doubling dose for *Hprt* mutations in the mouse, the doubling dose for *HPRT* mutations in humans, the mutation rate in mice, the number of loci involved, the risk from exposure of females, the extrapolation from mutation frequency to dominant disease states and possible influence of dose rates (Natarajan *et al.*, 1995). Although there was some attempt by the authors to quantitate uncertainty from these sources, such an estimate does not reflect uncertainty associated with reliance on limited (possibly unrepresentative) data, which could be considerably greater.

3.3.3.3 Other non-neoplastic effects

3.3.3.3.1 Humans

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[7] Value has been adjusted for intermittent (occupational) to continuous exposure, but not for reproductive lifetime, due to relatively short period of spermatogenesis.

Exposure–response for the neurological effects (including neurophysiological, neurobehavioural and histopathological effects) observed in workers exposed to ethylene oxide has not been well characterized. In case studies, reported levels of ethylene oxide have ranged from 4.2 to >700 ppm (7.7 to >1281 mg/m^3) (Gross *et al.*, 1979; Salinas *et al.*, 1981; Finelli *et al.*, 1983; Kuzuhara *et al.*, 1983; Zampollo *et al.*, 1984; Schroder *et al.*, 1985; Fukushima *et al.*, 1986; Ristow and Cornelius, 1986; Crystal *et al.*, 1988). In surveys, typical TWA exposures have ranged from <1 to 4.7 ppm (<1.8 to 8.6 mg/m^3), with peaks as high as 250 ppm (458 mg/m^3) ethylene oxide (Estrin *et al.*, 1987, 1990; Klees *et al.*, 1990). In individuals exposed to >700 ppm (1281 mg/m^3) ethylene oxide, sural nerve biopsies revealed axonal degeneration with mild changes in the myelin sheath; muscle biopsies revealed degeneration atrophy (Kuzuhara *et al.*, 1983).

Available data on other potential effects in humans associated with exposure to ethylene oxide (e.g., hematological, ocular and reproductive/developmental) are limited and inadequate for characterization of exposure–response.

3.3.3.3.2 Laboratory animals

Although ethylene oxide has induced a wide range of non-neoplastic effects in laboratory animals, it is those on the neurological and reproductive systems that occur at lowest concentrations.

With respect to neurological effects, abnormal gait and reduced locomotor activity (in two of five tests) were observed in small numbers of mice (n = 5) after subchronic exposure to ethylene oxide at concentrations ranging from 86 to 425 mg/m^3 (Snellings *et al.*, 1984a); at the highest concentration (425 mg/m^3), there were significant differences for toe and tail pinch reflexes and abnormal righting reflex. In another study in mice, however, there were no similar clinical signs (although neurobehavioural changes were not addressed specifically) in animals exposed to 50 or 100 ppm (92 or 183 mg/m^3) ethylene oxide for 2 years (NTP, 1987). In monkeys, histological alterations in the axons within the nucleus gracilis of the medulla oblongata and demyelination of the distal portion of the fasciculus gracilis within the medulla were observed following long-term exposure to ≥92 mg ethylene oxide/m^3 (Sprinz *et al.*, 1982; Lynch *et al.*, 1984b).

Effects of ethylene oxide on the testes of males in repeated-dose toxicity studies are the reproductive effects observed at lowest concentration, although there is a preliminary (unverifiable) report that there have been reductions in litter size and increased post-implantation losses in the F_0 animals at somewhat lower levels. Alterations in sperm morphology in rats (Mori *et al.*, 1991) and changes in sperm count and motility in monkeys (Lynch *et al.*, 1984c) were observed following exposure to 92 mg ethylene oxide/m^3. In rats, reductions in some reproductive parameters (i.e., number of pups born per litter, number of implantation sites per female) were observed in animals exposed before mating and during gestation to 100 ppm (183 mg/m^3) ethylene oxide (Snellings *et al.*, 1982b). Reportedly, reductions in litter size and increased post-implantation losses were observed in the F_0 and F_1 generations of rats exposed to

100 ppm (183 mg/m^3) ethylene oxide, although a full account is not yet available; these effects were also noted in F_0 animals exposed to 33 ppm (60.4 mg/m^3) ethylene oxide (Snellings, 1999).

Developmental effects that occurred at lowest concentrations were reductions in fetal body weight, without effects on skeletal length or ossification, following exposure of the dams to 100 ppm (183 mg/m^3) ethylene oxide during gestation (Snellings *et al.*, 1982a); this concentration appeared to have no overt effects on the dams.

In rats exposed chronically to ethylene oxide (Snellings *et al.*, 1984b), a slight (unspecified) reduction in body weight gain (in females) was reported at 33 ppm (60.4 mg/m^3). (There were only a limited number of non-neoplastic endpoints observed in this study.)

A slight increase in the prevalence of lens opacities has also been observed in monkeys exposed for 2 years to ≥92 mg ethylene oxide/m^3 (Lynch *et al.*, 1992). Hematological effects have also been observed in rats, mice and dogs exposed for various periods to greater concentrations of ethylene oxide than those addressed here (Jacobson *et al.*, 1956; Popp *et al.*, 1986; Katoh *et al.*, 1988, 1989; Fujishiro *et al.*, 1990; Mori *et al.*, 1990).

Based on available documented studies, therefore, non-neoplastic effects of ethylene oxide have been observed only at concentrations greater than those at which increases in tumours have been reported in other studies (i.e., the latter was observed at concentrations as low as 18.3 and 60.4 mg/m^3 in rats). In addition, in view of the likely critical role of the genotoxicity of ethylene oxide, for which the weight of evidence is consistent and convincing in the induction of tumours, cancer is clearly the critical endpoint for quantitation of exposure–response for risk characterization, and measures based on this endpoint will be protective for other reported effects. For example, a Tolerable Concentration based upon observed effects on the sperm (i.e., reduced count and motility) and brain (i.e., nerve dystrophy and demyelination) in monkeys exposed chronically to ethylene oxide (Sprinz *et al.*, 1982; Lynch *et al.*, 1984b,c; Setzer *et al.*, 1996) or upon reproductive effects (i.e., reduced number of pups per litter and implantation sites per female) observed in rats exposed subchronically to ethylene oxide, prior to and during mating as well as during gestation (Snellings *et al.*, 1982b), would be in the range of tens of µg/m^3.

3.3.4 Human health risk characterization

For substances such as ethylene oxide, where there is a strong likelihood that the mode of action for the induction of tumours involves direct interaction with genetic material, estimates of exposure are compared with quantitative estimates of carcinogenic potency (Exposure Potency Index, or EPI) to characterize risk and to provide guidance in establishing priorities for further action (i.e., analysis of options to reduce exposure) under CEPA.

The lowest TC_{05} in the study in rats with optimal characterization of exposure–response (Snellings *et al.*, 1984b; Garman *et al.*, 1985; Garman and Snellings, 1986) and in mice (NTP, 1987) was 2.2 mg/m^3 for the development of mononuclear leukemias in F344 female rats exposed via inhalation to ethylene oxide; the 95% LCL was 1.5 mg/m^3 (Table 6). The margins between carcinogenic potency and the extremely limited data on measured and predicted concentrations of ethylene oxide in ambient (and indoor) air in Canada (and elsewhere) are presented in the table below. On this basis, the priority for investigation of options to reduce exposure in the vicinity of point sources is considered to be high. However, it should be noted that this is based on concentrations modelled, taking into account information on releases, which have not been validated by monitoring data.[8] Based upon margins between censored mean concentrations for monitoring data from a multimedia exposure study conducted in Canada, the priority for investigation of options to reduce exposure to ethylene oxide is moderate to high, although it should be noted that this is based on detection in a very small proportion of samples in the study.

Concentration of ethylene oxide	**Potency (TC_{05}) : [95% LCL] (2200 µg/m^3) : [1500 µg/m^3]**	**Margin between potency and concentration**	**Exposure Potency Index (EPI)**	**Priority for further action (Health Canada, 1994)**
0.0062 µg/m^3; concentration in ambient air in southern Ontario predicted from ChemCAN fugacity model	(2200) : [1500]	(350 000) : [240 000]	(2.9×10^{-6}) : [4.2×10^{-6}]	(Moderate) : [Moderate]
0.34 µg/m^3; censored mean concentration in ambient air from multimedia survey in Canada (Health Canada, 1999a)	(2200) : [1500]	(6500) : [4400]	(1.5×10^{-4}) : [2.3×10^{-4}]	(Moderate) : [High]
0.17 µg/m^3; censored mean concentration in indoor air from multimedia survey in Canada (Health Canada, 1999a)	(2200) : [1500]	(13 000) : [8800]	(7.7×10^{-5}) : [1.1×10^{-4}]	(Moderate) : [Moderate]
2.12 µg/m^3; predicted maximum average daily concentration in ambient air in the vicinity of Canadian hospitals	(2200) : [1500]	(1040) : [710]	(9.6×10^{-4}) : [1.4×10^{-3}]	(High) : [High]
4.9 µg/m^3; maximum concentration in ambient air from multimedia survey in Canada (Health Canada, 1999a)	(2200) : [1500]	(450) : [310]	(2.2×10^{-3}) : [3.2×10^{-3}]	(High) : [High]
4.0 µg/m^3; maximum concentration in indoor air from multimedia survey in Canada (Health Canada, 1999a)	(2200 µg/m^3) : [1500 µg/m^3]	(550) : [375]	(1.8×10^{-3}) : [2.7×10^{-3}]	(High) : [High]

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[8] For comparison, based on a maximum mean concentration measured at one site in Los Angeles, California (956 lg/m^3; Havlicek *et al.*, 1992), the EPI value would be 0.43.

Concentration of ethylene oxide	Potency (TC_{05}) : [95% LCL] (2200 µg/m^3) : [1500 µg/m^3]	Margin between potency and concentration	Exposure Potency Index (EPI)	Priority for further action (Health Canada, 1994)
20.1 µg/m^3; predicted maximum 1-hour ground-level concentration in ambient air in the vicinity of an ethylene oxide production facility in Canada	(2200) : [1500]	(110) : [75]	(9.1×10^{-3}) : [1.3×10^{-2}]	(High) : [High]
2 µg/m^3; predicted maximum average annual concentration in ambient air in the vicinity of a hospital in Florida (Tutt and Tilley, 1993)	(2200) : [1500]	(1100) : [750]	(9.1×10^{-4}) : [1.3×10^{-3}]	(High) : [High]
11 µg/m^3; predicted maximum average annual concentration in ambient air in the vicinity of a sterilization facility in Florida (Tutt and Tilley, 1993)	(2200) : [1500]	(200) : [140]	(5.0×10^{-3}) : [7.1×10^{-3}]	(High) : [High]

3.3.5 Uncertainties and degree of confidence in human health risk characterization

There are considerable uncertainties in the assessment of human exposure to ethylene oxide resulting from the paucity of information concerning current levels in media to which the general population of Canada is currently exposed. There is a high degree of certainty that ethylene oxide has been and is being discharged to the atmosphere in Canada from chemical manufacturing facilities and from hospital sterilizers. There is a moderate degree of certainty that these emissions have been decreasing in recent years, but this conclusion is based on voluntary reporting of emission estimates and has not been validated by comparison of historic and current data concerning concentrations in the outdoor air in the vicinity of point sources of atmospheric discharge. In addition, the potential impact of a new ethylene oxide/glycol production facility in Scotford, Alberta, on trends of future releases is not known. There is a high degree of uncertainty regarding the range of concentrations of ethylene oxide in the atmosphere or in air in the vicinity of point sources in Canada, as relevant monitoring data have not been identified. Rather estimates included herein are restricted to those based on unvalidated fugacity and dispersion modelling.

There is a very high degree of uncertainty regarding concentrations of ethylene oxide in the indoor air of Canadian residences and public places. Other than environmental tobacco smoke, potential indoor sources of ethylene oxide have not been identified. There is a moderate degree of certainty that smokers have higher daily intakes of ethylene oxide than non-smokers, but data on the amounts of ethylene oxide in the mainstream and sidestream smoke of Canadian cigarettes were not identified. There is a moderate degree of certainty that ethylene oxide is not released in significant amounts from consumer products in which this substance is incorporated during manufacture.

There is a moderate degree of certainty that the consumption of drinking water does not contribute significantly to the intake of ethylene oxide in Canada. Although no data were identified concerning concentrations in surface water, groundwater or drinking water in Canada, ethylene oxide has been detected only very infrequently in water in the United States. The physical/chemical properties of ethylene oxide and the fact that it is released to the atmosphere support the conclusion that concentrations in water in Canada would be negligible.

There is a very high degree of uncertainty concerning the levels of ethylene oxide in foods consumed in Canada, since relevant monitoring data were not identified. There is a high degree of certainty that among potential food sources, spices are most likely to have the highest concentrations, as fumigation of spices with ethylene oxide is permitted in Canada. Monitoring of ethylene oxide concentrations in Canadian foodstuffs is clearly desirable to improve estimates based on limited and possibly unrepresentative data on levels of ethylene oxide in foodstuffs from other countries, and highly uncertain values for consumption rates indicate that food may be a significant source of exposure.

The degree of confidence in the database on the toxicity of ethylene oxide is moderate. While the database on non-cancer toxicity in laboratory animals is limited, there is a high degree of confidence that cancer and heritable genotoxicity occur at lowest concentrations, and risk management measures developed on the basis of exposure–response for these effects will be protective for other adverse effects in the general population.

The carcinogenicity of ethylene oxide in humans has been investigated in a number of studies, the largest of which involved a cohort of more than 18 000 individuals. However, limitations of these investigations prevent adequate consideration of traditional criteria for causality (particularly with respect to periods of follow-up in investigations of greatest sensitivity). Similarly, epidemiological studies on cytogenetic changes and reproductive effects in human populations are inadequate to allow any inference concerning causality to be drawn.

While there is a high degree of certainty that the genotoxicity of ethylene oxide plays an important role in the carcinogenicity of this substance and that the metabolism and mode of action of ethylene oxide in humans and laboratory animals do not differ qualitatively, the mode of action in inducing cancer or heritable genotoxic effects has not been clearly delineated. Possible quantitative variations between humans and animals have also not been elucidated.

Meaningful direct comparison of carcinogenic potency in laboratory animals with that in humans is precluded due to limitations of the epidemiological database, the inadequacy of available information on interspecies variations in kinetics, metabolism and mode of action to serve as a basis for characterization of site concordance between animals and humans, and the extremely wide range of the confidence limits on the SMRs in the epidemiological studies.

There is some uncertainty concerning the relevance to humans of mononuclear cell leukemias in F344 rats, since this type of tumour is specific to this strain of rat, it arises spontaneously with a significant frequency in older unexposed animals, and its etiology has not been definitively identified. However, TC_{05}s for the tumours with next greatest potency for the studies in rats and mice with optimum characterization of exposure–response and resulting EPIs would be approximately only 3-fold greater, and priorities for further action would remain the same. The 95% LCL on the TC_{05} for mononuclear leukemia in female rats was 1.5 mg/m^3, versus the maximum likelihood estimate of 2.2 mg/m^3. Based upon the highest TC_{05} identified from the study in which exposure–response was best characterized (i.e., 31.0 mg/m^3 for primary brain tumours in female F344 rats), the resulting EPIs would be approximately 14-fold lower than those derived (in Section 3.3.4) on the basis of the mononuclear cell leukemias in female F344 rats.

3.4 Proposed conclusions

CEPA 11(a): Based on available data, it is unlikely that ethylene oxide is entering or may enter the environment in a quantity or concentration or under conditions having or that may have an immediate or long-term harmful effect on the environment. Therefore, ethylene oxide is not proposed to be considered "toxic" as defined under Paragraph 11(a) of CEPA.

CEPA 11(b): Based on available data, it is unlikely that ethylene oxide is entering or may enter the environment in a quantity or concentration or under conditions constituting or that may constitute a danger to the environment on which human life depends. Therefore, ethylene oxide is not proposed to be considered "toxic" as defined under Paragraph 11(b) of CEPA.

CEPA 11(c): Based on available data, it has been concluded that ethylene oxide is entering the environment in a quantity or concentration or under conditions constituting or that may constitute a danger in Canada to human life or health. Therefore, ethylene oxide is proposed to be considered "toxic" as defined under Paragraph 11(c) of CEPA. This approach is consistent with the objective that exposure to compounds where induction of cancer through direct interaction with genetic material cannot be ruled out be reduced wherever possible and obviates the need to establish an arbitrary "*de minimis*" level of risk for the determination of "toxic" under CEPA. On the basis of limited monitoring data and predicted concentrations of ethylene oxide in air, the priority for investigation of options to reduce exposure, particularly in the vicinity of point sources, is considered to be high.

Proposed overall conclusion: Based on critical assessment of relevant information, it is proposed that ethylene oxide be considered "toxic" as defined in Section 11 of CEPA.

3.5 Considerations for follow-up (further action)

Based on comparison of extremely limited monitoring data and primarily predicted concentrations of ethylene oxide in air with tumorigenic potency, it is recommended that options to reduce exposure, particularly in the vicinity of point sources, be investigated. It is also recommended that there be additional investigation of the magnitude of exposure of populations in the vicinity of point sources as a basis for risk management.

Table 1: Physical and chemical properties of ethylene oxide

Property	Parameter	Reference
Melting point (°C)	–111.6	WHO (1985)
Boiling point (°C)	10.7	WHO (1985)
Density (g/mL @ 20°C)	0.8795	WHO (1985)
Vapour pressure (kPa)	66 @ 0°C 100 @ 10°C 146 @ 20°C 208 @ 30°C	Verschueren (1983) KemI (1995)
Henry's law constant (Pa∀m^3/mol)	14	BUA (1995)
	12.16	Conway *et al.* (1983)
	19.86	DMER and AEL (1996)
Sorption partition coefficient (log K_{oc})	1.204	KemI (1995)
Octanol/water partition coefficient (log K_{ow})	–0.22 –0.30	WHO (1985)
Solubility in water (g/L)	infinitely soluble	WHO (1985)
Conversion factors	1 ppm in air = 1.83 mg/m^3 1 mg/m^3 = 0.55 ppm	KemI (1995)

Table 2: Physical and chemical properties of ethylene oxide used in the fugacity modelling (DMER and AEL, 1996)

Property	Range of values	Selected value
Molecular weight (g/mol)		44.05
Vapour pressure (kPa @ 25°C)	107.41–192.85 (at temperatures between 12 and 25°C)	173.27
Water solubility (mg/L)	3.83×10^8 to miscible	miscible
Log K_{ow}	–0.26 to –0.792	–0.3
Henry's law constant (Pa∀m^3/mol)	12.16–19.86	19.86
Half-life — air (hours)	917–9168	1700
Half-life — water (hours)	288–336	550
Half-life — soil (hours)	240–480	550
Half-life — sediment (hours)	—	1700

Note: To ensure conservative estimates, some half-life values used for modelling were longer than actual estimated values.

Table 3: Input parameters to the SCREEN3 model (U.S. EPA, 1995)

Input parameter	**Value**
Gas concentrations	250 to 1500 mg/L of chamber volume
Exposure time	45 minutes to 20 hours (often less than 5 hours)
Total cycle time	14–16 hours; one cycle per day
Rate of use	91–137 kg per year per hospital with sterilization facilities
Typical wind speed	1.5 m/s
Aeration release	Average hospital (~400 beds) would have a peak ethylene oxide release during aeration of approximately 0.36 kg
Stack height	18.3 m (~5 stories high) average; range between 12.2 and 30.5 m
Sterilizer volume	0.849 m^3
Emission rate	0.45 kg cycle; 0.36 kg in the first hour
Downwash	Downwash effects considered assuming building is 1.5 m below the stack tip and that building width is 3 times the height
Stability category	F

Notes:

1. Momentum and buoyancy effects are not considered.
2. The model estimated a 24-hour average ethylene oxide concentration in ppb.

Table 4: Cytogenetic effects in humans (modified from IARC, 1994)

Number exposed (number of controls)	Exposure time (years)		Ethylene oxide level in air (ppm)[1]		Cytogenetic observations[2]			Reference
	Range	Mean	Range	Mean (TWA)	CA	SCE	MN	
75 (0)				±50	+	+		Abrahams (1980)
33 (0)	1–14		±0.05–8	±0.01[3]	(+)			Clare *et al.* (1985)
13 (site I)			0.5[4]		–	–		Stolley *et al.* (1984); Galloway *et al.* (1986)
22 (site II)			5–10[4]		–	+		
25–26 (site III)			5–20[4]		+	+		
(171 controls total)								
12 (12)			±36			+		Garry *et al.* (1979)
14 (14)			<0.07–4.3[4]			–		Hansen *et al.* (1984)
18 (factory I)	0.5–8	3.2		<1	+	–	+[5]	Hogstedt *et al.* (1983)
10 (factory II)	0.5–8	1.7		<1	+	–		
(20 controls total)								
18 (sterilization centres) (10)	1–8		0–2.6		+			Karelová *et al.* (1987)
14 (laboratory – 1983) (10)	1–15		0–4		+			
11 (laboratory – 1984) (10)	1–15		0–2.3		–			
21 (production workers) (20)	2–17		0–3.7		+			
15 (smokers) (7)	0.5–10	5.7	20–123			+		Laurent *et al.* (1984)
10 (non-smokers) (15)	0.5–10	4.5	20–123			+		
10 (10)		3	60–69[4]		+	+		Lerda and Rizzi (1992)
9 (low dose) (48)		4	2.7–10.9	2.7	+	–		Major *et al.* (1996)
27 (high dose) (10)		15	2.7–82	5.5	+	+		
34 (23)		8[6]	<0.1–2.4[4]	<0.3	–	+	–	Mayer *et al.* (1991)
12	1–8	4	0.5–1		–			Pero *et al.* (1981)
5	0.8–3	1.6	5–10		+			
(11 controls total)								
11 (smokers)			0.5–417[7]			–		Popp *et al.* (1994)
14 (non-smokers)			0.5–208[7]			–		
(10 controls total)								
75 (22)	3–14	7	2–5[4]		+		+	Ribeiro *et al.* (1994)
56 (141)	1–10		1–40[4]		+	+		Richmond *et al.* (1985)

Number exposed (number of controls)	Exposure time (years)		Ethylene oxide level in air (ppm)[1]		Cytogenetic observations[2]			Reference
	Range	Mean	Range	Mean (TWA)	CA	SCE	MN	
22 (22)	0.6–4	3	0.2–0.5[4]	0.35	(+)	+		Sarto *et al.* (1984)
19 (19)	1.5–15	6.8	3.7–20[4]	10.7	+	+		
10 (10)			0–9.3[4]	1.84		+		Sarto *et al.* (1987)
9 (27 controls total)	0.5–12	5	0.025–0.38[4]				–	Sarto *et al.* (1990)
3			>0.38[8]				+[9]	
5 (10 controls total)	0.1–4	2		0.025		–	–[10]	Sarto *et al.* (1991)
5	4–12	8.6	<1–4.4	0.38		+	–[10]	
32 (8 controls total)		5.1	0–0.3[4]	0.04		+	–	Schulte *et al.* (1992)
11		9.5	0.13–0.3[4]	0.16		+	–	
9 (hospital workers) (8)	2–6	4	20–25		+	+	–	Tates *et al.* (1991)
15 (factory workers) (15)	3–27	12	17–33		+	+	+	
7 (7 controls total)	accidental		28–429[4]			–	–	Tates *et al.* (1995)
7	<5		<0.005–0.02			–	–	
7	>15		<0.005–0.01			–	–	
9 (low exposure)				13[11]		–		Yager *et al.* (1983)
5 (high exposure)				501[11]		+		
(13 controls total)								
19 (35 controls total)	1–5		<0.05–8	<0.05	–			van Sittert *et al.* (1985)
17	6–14		<0.05–8	<0.05	–			

[1] 1 ppm = 1.83 mg ethylene oxide/m³.

[2] CA = chromosomal aberrations; SCE = sister chromatid exchange; MN = micronucleus.

[3] Calculated by linear extrapolation.

[4] TWA (8-hour).

[5] Positive for erythroblasts and polychromatic erythrocytes (negative for lymphocytes).

[6] Maximum years exposed.

[7] Peak concentrations.

[8] Exposed acutely from sterilizer leakage in addition to chronic exposure

[9] Nasal mucosa.

[10] Buccal cells.

[11] Average 6-month cumulative exposure (mg).

Table 5: Summary of risk measures for selected cancers (stomach, pancreas, brain, hematopoietic) from epidemiological studies

Cancer	Exposure to ethylene oxide	Risk measure[1]	Reference
Stomach	male and female ethylene oxide production workers (two plants) and medical equipment sterilizers	SMR = 546: *10*	Hogstedt (1988)
Blood and lymphatic		SMR = 459: *9*	
Leukemia		SMR = 921: *7*	
Stomach	workers from older production plant	SMR = 707: *9*	
Leukemia	workers from older production plant	SMR = 703: *3*	
	10-year update of male workers producing or using ethylene oxide (excluding chlorohydrin production) studied by Greenberg *et al.* (1990)		Teta *et al.* (1993)
Stomach	entire cohort	SMR = 160 (95% CI = 69–315): *8*	
Pancreas	entire cohort	SMR = 61 (95% CI = 17–156): *4*	
Brain and nervous system	entire cohort	SMR = 150 (95% CI = 55–327): *6*	
Leukemia and aleukemia	entire cohort	SMR = 106 (95% CI = 35–248): *5*	
Stomach	intermediate-exposure subgroup	SMR = 364 (95% CI = 102–957): *4**	
Stomach	low-exposure subgroup	SMR = 222 (95% CI = 61–575): *4*	
	male and female workers in facilities producing sterilized medical equipment and spices		Steenland *et al.* (1991)
Hematopoietic cancers	those with >20 years since first exposure	SMR = 1.76 (95% CI = 0.94–3.01): *34*	
Hematopoietic cancers	males only	SMR = 1.55 (p = 0.05): *27**	
Lymphosarcoma/reticulosarcoma	males only	SMR = 2.6 (p = 0.05): *7**	
Non-Hodgkin's lymphoma	males only	SMR = 2.16: *7*	
Hematopoietic cancers	males with >7 years exposure and >20 years since first exposure	SMR = 2.63 (95% CI = 1.05–5.42): *7**	
Hematopoietic cancers	workers with highest cumulative exposure	SMR = 124 (95% CI = 66–213): *13*	Stayner *et al.* (1993)
Non-Hodgkin's lymphoma	workers with highest cumulative exposure	SMR = 192 (95% CI = 77–395): *7*	
Leukemia/aleukemia	workers with highest cumulative exposure	SMR = 75 (95% CI = 15–218): *3*	
Hematopoietic cancers	males with highest cumulative exposure	SMR = 196 (95% CI = 101–343): *12**	
Hematopoietic cancers	males with moderate cumulative exposure	SMR = 143 (95% CI = 62–283): *8*	

Cancer	Exposure to ethylene oxide	Risk measure[1]	Reference
Hematopoietic cancers	males with lowest cumulative exposure	SMR = 95 (95% CI = 26–243): *4*	
Hematopoietic cancers	workers with >20 years since first exposure	SMR = 155 (95% CI = 77–277): *11*	
Lympho-/hematopoietic cancers	male and female workers sterilizing medical equipment	SIR = 1.78 (95% CI = 0.65–3.88): *6*	Hagmar *et al.* (1995)
Leukemia	male and female workers sterilizing medical equipment	SIR = 2.44 (95% CI = 0.3–8.81): *2*	
Leukemia Brain	workers having a minimum 10 years latency (but excluding those with cumulative exposure <0.13 ppm-years)	SIR = 7.14 (95% CI = 0.87–25.8): *2* SIR = 3.80 (95% CI = 0.78–11.1): *3*	
Hodgkin's disease	male workers at a chemical manufacturing plant	SIR = 497 (95% CI = 238–915): *10**	Swaen *et al.* (1996)
Hodgkin's disease	nested case–control analysis of male workers at the chemical manufacturing plant	OR = 8.5 (95% CI = 1.4–39.9): *3*^{2*}	
Leukemia	male workers at chemical plants	SMR = 0.85 (95% CI = 0.10–3.07): *2*	Kiesselbach *et al.* (1990)
Stomach	male workers at chemical plants	SMR = 1.38 (95% CI = 0.75–2.31): *14*	
Leukemia	males and females at ethylene oxide production/use facilities	SMR = 2.25 (95% CI = 0.47–6.59): *3*	Gardner *et al.* (1989)
Stomach	males and females at hospitals	SMR = 1.19 (95% CI = 0.15–4.32): *2*	
Pancreas Brain and central nervous system Hodgkin's disease	male petroleum plant workers	SMR = 377 (95% CI = 76–1102): *3* SMR = 285 (95% CI = 32–1030): 2 SMR = 570 (95% CI = 64–2058): *2*	Morgan *et al.* (1981)
Brain and central nervous system Lympho-/hematopoietic	male workers involved in the production of ethylene chlorohydrin and propylene chlorohydrin	SMR = 123 (95% CI = 25–358): *3* SMR = 129 (95% CI = 62–238): *10*	Olsen *et al.* (1997)
Lympho-/hematopoietic	male workers involved in the production of ethylene chlorohydrin	SMR = 149 (95% CI = 60–307): *7*	
Lympho-/hematopoietic	male workers involved in the production of ethylene chlorohydrin (analysis included a 25-year latency period)	SMR = 194(95% CI = 71–423): *6*	
Hematopoietic cancers	male workers licensed to handle ethylene oxide and other chemicals	SMR = 250 (95% CI = 91–545): *6*	Bisanti *et al.* (1993)
Lympho/reticulosarcoma	male workers licensed to handle ethylene oxide and other chemicals	SMR = 682 (95% CI = 186–1745): *4**	
Leukemia/aleukemia	male workers licensed to handle ethylene oxide and other chemicals	SMR = 193 (95% CI = 23–699): *2*	
Stomach	male workers licensed to handle ethylene oxide and other chemicals	SMR = 122 (95% CI = 40–287): *5*	
Pancreas	male workers licensed to handle ethylene oxide and other chemicals	SMR = 254 (95% CI = 52–744): *3*	
Hematopoietic cancers	male workers licensed to handle ethylene oxide only	SMR = 700 (95% CI = 227–1637): *5**	
Lympho/reticulosarcoma	male workers licensed to handle ethylene oxide only	SMR = 1693 (95% CI = 349–4953): *3**	

Cancer	**Exposure to ethylene oxide**	**Risk measure**[1]	**Reference**
Leukemia/aleukemia	male workers licensed to handle ethylene oxide only	SMR = 650 (95% CI = 79–2349):*2*	
Leukemia	male and female workers using ethylene oxide as a sterilant	SMR = 1.85 (p = 0.42): *1*	Norman *et al.* (1995)
Pancreas	male and female workers using ethylene oxide as a sterilant	SMR = 3.92 (p = 0.09): *2*	
Leukemia	meta-analysis of reports published between 1979 and 1993	sSMR = 1.06 (95% CI = 0.73–1.48): *31*	Shore *et al.* (1993)
Non-Hodgkin's lymphoma		sSMR = 1.35 (95% CI = 0.93–1.90): *31*	
Stomach		sSMR = 1.28 (95% CI = 0.98–1.65): *57*	
Pancreas		sSMR = 0.98 (95% CI = 0.69–1.36): *34*	
Brain and central nervous system		sSMR = 0.89 (95% CI = 0.55–1.36): *19*	
Leukemia	update of Shore *et al.* analyses, but including two additional studies	mSMR = 1.08 (95% CI = 0.61–1.93): *35*	Teta *et al.* (1999)
Non-Hodgkin's lymphoma		mSMR = 1.34 (95% CI = 0.96–1.89): *33*	
Stomach		mSMR = 1.23 (95% CI = 0.71–2.13): *59*	
Pancreas		mSMR = 0.95 (95% CI = 0.69–1.31): *37*	
Brain		mSMR = 0.96 (95% CI = 0.49–1.91): *25*	

[1] Unless otherwise noted, value in italics is the number of observed deaths or cases. Asterisk (*) indicates increase reported a statistically significant.

[2] Number of cases exposed to ethylene oxide.

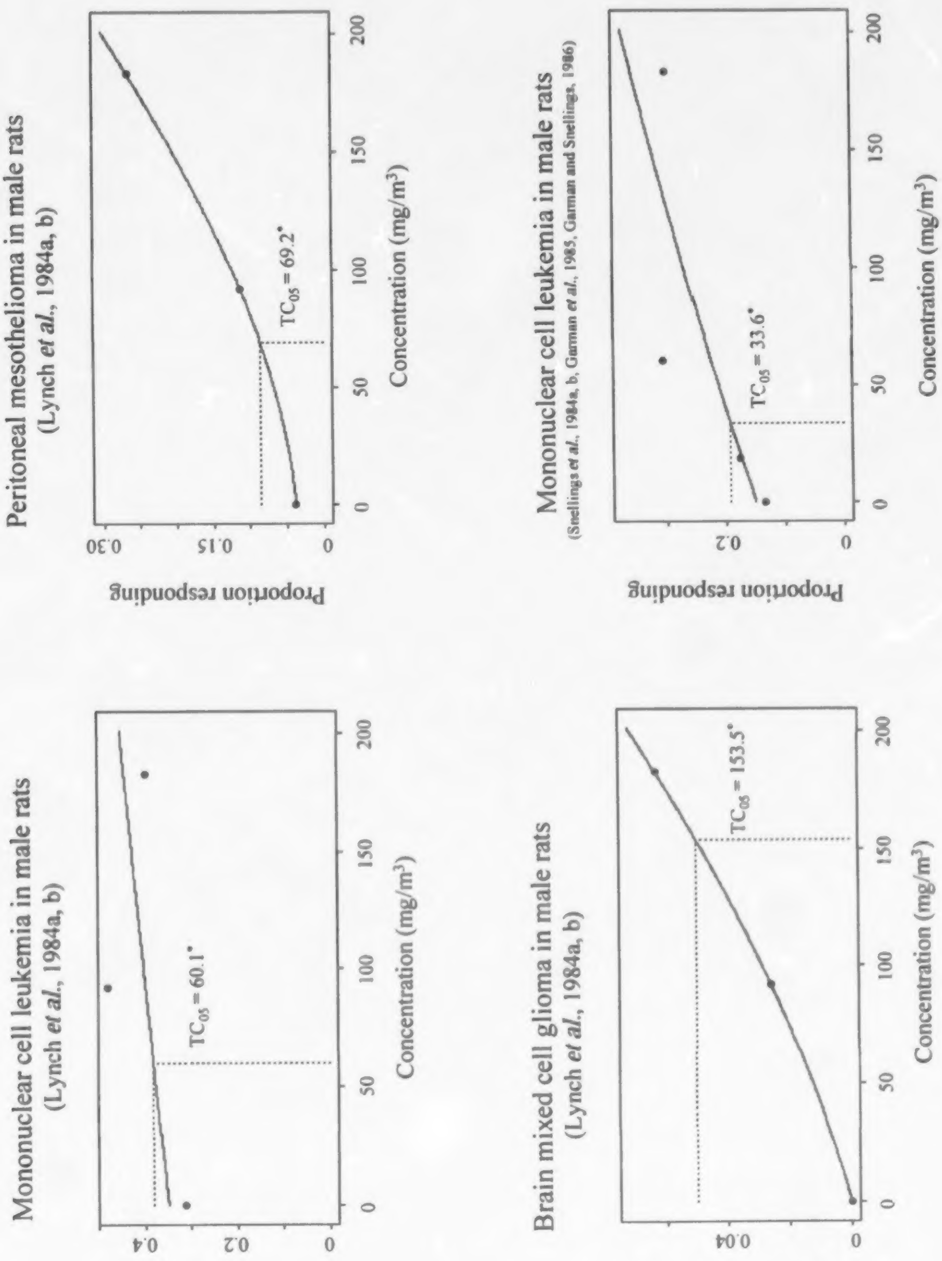
Table 6: TC_{05}s for ethylene oxide

Tumour incidence	**TC_{05} (mg/m^3)**	**LCL on TC_{05} (mg/m^3)**	**Chi-square**	**df**	**p-value**
Male rats exposed to 0, 92 or 183 mg ethylene oxide/m^3, 7 hours/day, 5 days/week (Lynch *et al*, 1984a,b)[1]					
Incidence of mononuclear cell leukemia: 24/77, 38/70, 30/76	12.5	5.1	3.5	1	0.06
Incidence of peritoneal mesothelioma: 3/78, 9/79, 21/79	14.4	6.1	0	0	–
Incidence of brain mixed cell glioma: 0/76, 2/77, 5/79	31.9	18.3	0	1	1.0
Male and female rats exposed to 0, 18.3, 60.4 or 183 mg ethylene oxide/m^3, 6 hours/day, 5 days/week (Snellings *et al*, 1984b; Garman *et al.*, 1985; Garman and Snellings, 1986)[2]					
Incidence of mononuclear leukemia in males: 13/97, 9/51, 12/39, 9/30	6.0	3.1	2.2	2	0.34
Incidence of mononuclear leukemia in females: 11/116, 11/54, 14/48, 15/26	2.2	1.5	0.58	2	0.75
Incidence of peritoneal mesothelioma in males: 2/97, 2/51, 4/39, 4/30	10.8	5.6	0.78	2	0.68
Incidence of primary brain tumours in males: 1/181, 1/92, 5/85, 7/87	17.5	10.8	1.6	2	0.50
Incidence of primary brain tumours in females: 1/188, 1/94, 3/92, 4/80	31.0	16.1	0.45	2	0.80
Male and female mice exposed to 0, 92 or 183 mg ethylene oxide/m^3, 6 hours/day, 5 days/week (NTP, 1987)[2]					
Incidence of lung carcinoma in males: 6/50, 10/50, 16/50	10.2	4.1	0	0	–
Incidence of lung carcinoma in females: 0/49, 1/48, 7/49	19.8	10.3	0.34	2	0.84
Incidence of malignant lymphoma in females: 9/49, 6/48, 22/49	12.2	6.3	3.5	1	0.06
Incidence of uterine adenocarcinoma: 0/49, 1/47, 5/47	22.7	11.4	0.07	2	0.97
Incidence of mammary adenocarcinoma and adenosquamous carcinoma in females: 1/49, 8/48, 6/49	10.4	6.0	3.0	1	0.08
Incidence of Harderian cystadenoma in males: 1/43, 9/44, 8/42	6.7	4.2	2.0	1	0.16
Incidence of Harderian cystadenoma in females: 1/46, 6/46, 8/47	9.1	5.5	0.30	1	0.58

[1] For this study, the resulting TC_{05}s (and LCL on TC_{05}s) were multiplied by (7 hours per day/24 hours per day) × (5 days per week/7 days per week) to adjust for intermittent to continuous exposure.

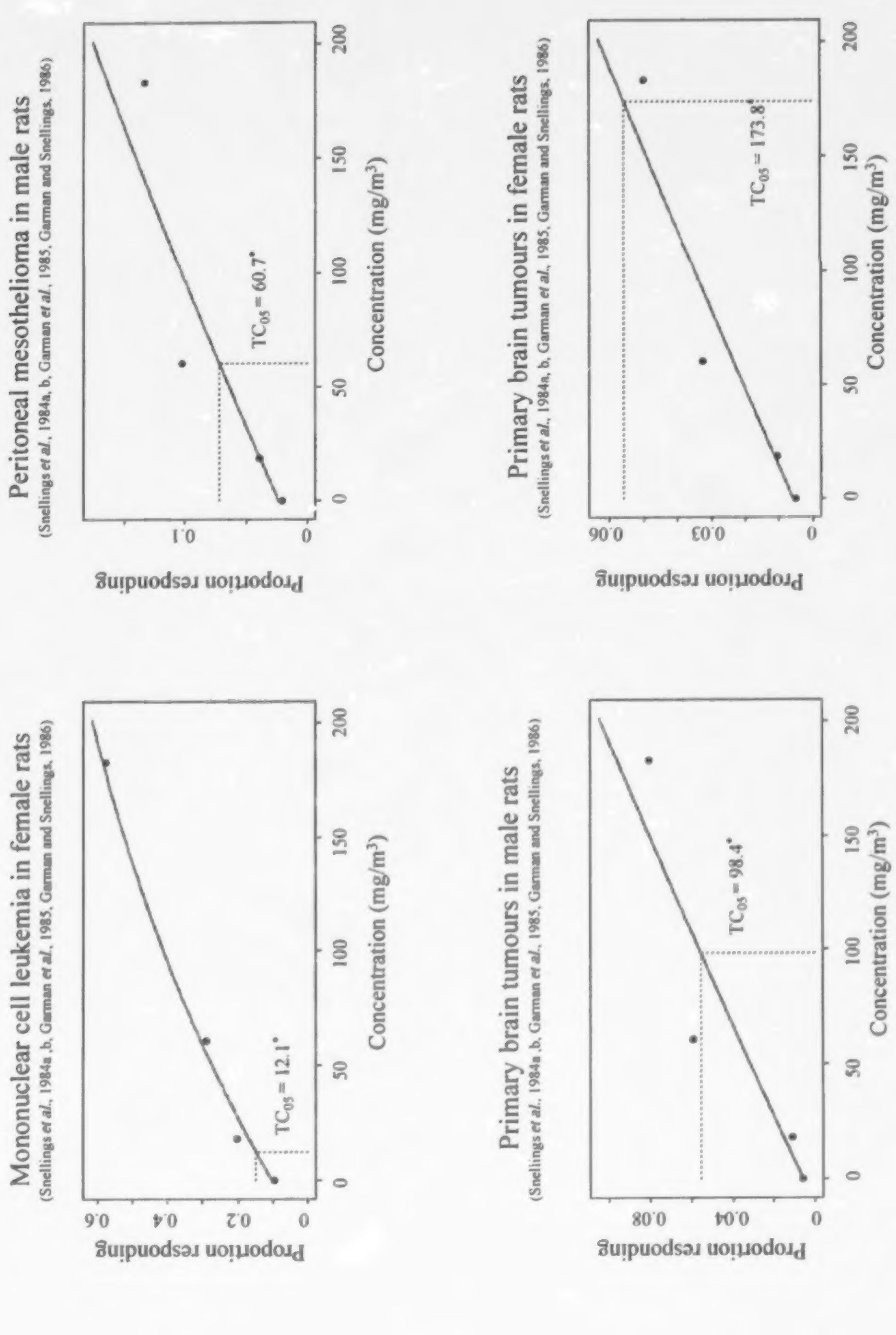
[2] For this study, the resulting TC_{05}s (and LCL on TC_{05}s) were multiplied by (6 hours per day/24 hours per day) × (5 days per week/7 days per week) to adjust for intermittent to continuous exposure.

Figure 2: TC_{05}s for ethylene oxide



* TC_{05} unadjusted for lifetime dosing

Figure 2 (continued)



Mononuclear cell leukemia in female rats
(Snellings *et al.*, 1984a ,b, Garman *et al.*, 1985, Garman and Snellings, 1986)

Peritoneal mesothelioma in male rats
(Snellings *et al*, 1984a, b, Garman *et al.*, 1985, Garman and Snellings, 1986)

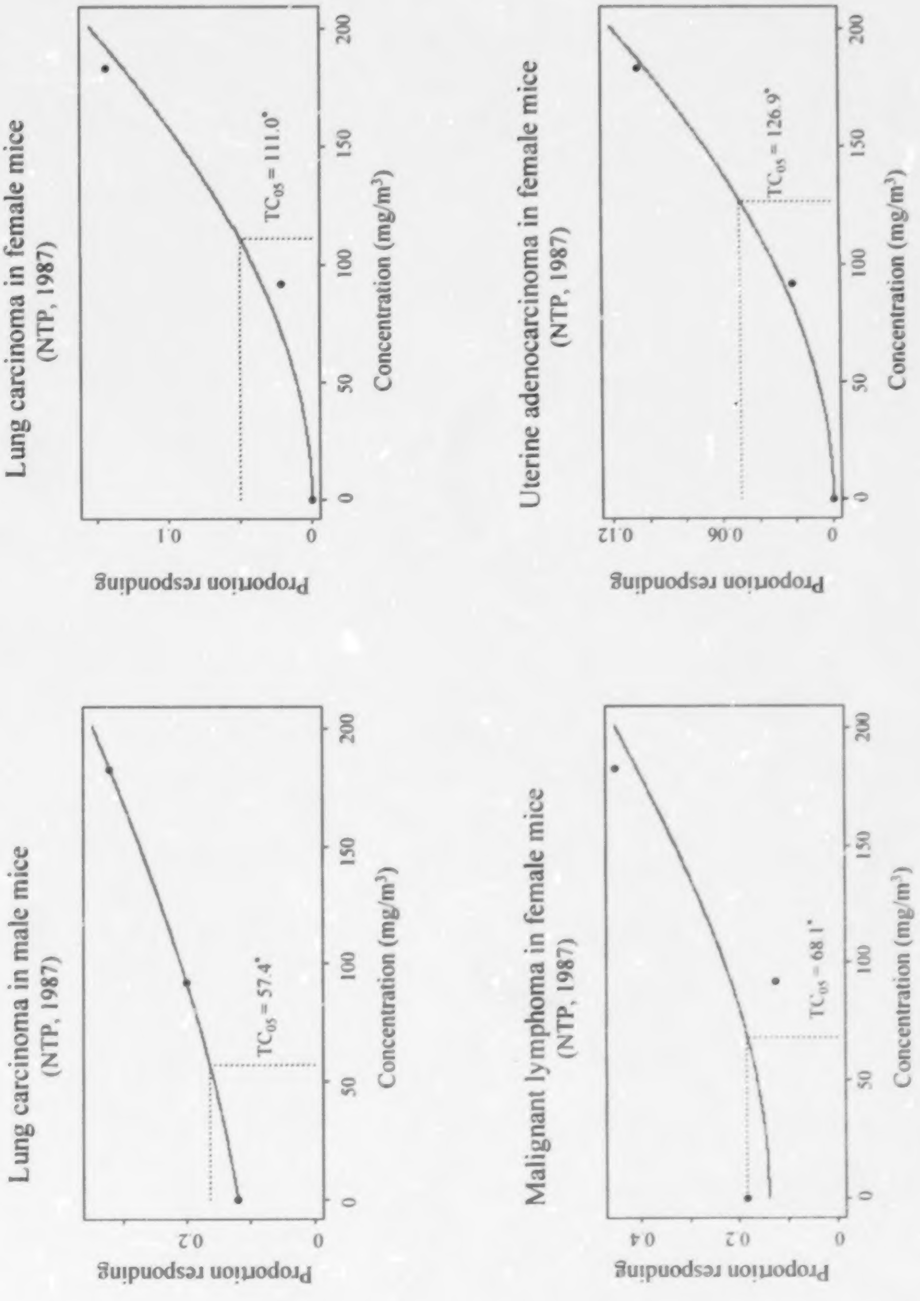
Primary brain tumours in male rats
(Snellings *et al.*, 1984a ,b, Garman *et al.*, 1985, Garman and Snellings, 1986)

Primary brain tumours in female rats
(Snellings *et al.*, 1984a, b, Garman *et al.*, 1985, Garman and Snellings, 1986)

Proportion responding
0
0.03
0.06
Concentration (mg/m^3)
0
50
100
150
200
TC$_{05}$ = 173.8

* TC$_{05}$ unadjusted for lifetime dosing

Figure 2 (continued)


Lung carcinoma in female mice (NTP, 1987)

Uterine adenocarcinoma in female mice (NTP, 1987)

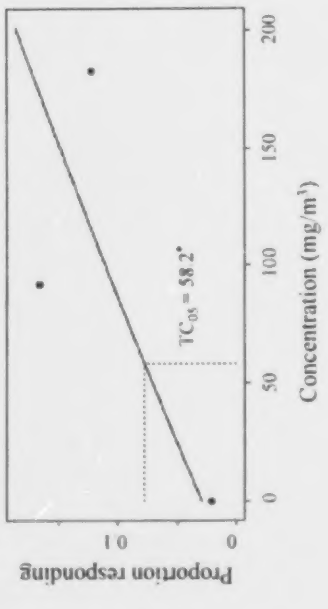
Lung carcinoma in male mice (NTP, 1987)

Malignant lymphoma in female mice (NTP, 1987)

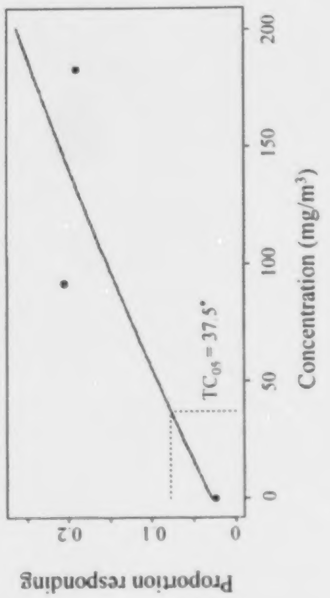
* TC_{05} unadjusted for lifetime dosing

Figure 2 (continued)

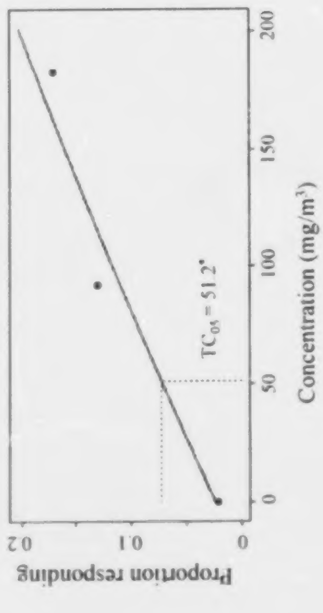
Mammary adeno & adenosquamous carcinoma in female mice (NTP, 1987)



Harderian cystadenoma in male mice (NTP, 1987)



Harderian cystadenoma in female mice (NTP, 1987)



* TC$_{05}$ unadjusted for lifetime dosing

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APPENDIX A: Search strategies employed for identification of relevant data

Environmental assessment

Data relevant to the assessment of whether ethylene oxide is "toxic" to the environment under CEPA were identified from existing review documents, published reference texts and on-line searches conducted between January and May 1996 of the following databases: Aqualine (1990–1996), ASFA (Aquatic Sciences and Fisheries Abstracts, Cambridge Scientific Abstracts; 1996), BIOSIS (Biosciences Information Services; 1990–1996), CAB (Commonwealth Agriculture Bureaux; 1990–1996), CESARS (Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources; 1996), Chemical Abstracts (Chemical Abstracts Service, Columbus, Ohio; 1990–1996), CHRIS (Chemical Hazard Release Information System; 1964–1985), Current Contents (Institute for Scientific Information; 1990–1992, 1996), ELIAS (Environmental Library Integrated Automated System, Environment Canada library; January 1996), Enviroline (R.R. Bowker Publishing Co.; November 1995 – May 1996), Environmental Abstracts (1975 – February 1996), Environmental Bibliography (Environmental Studies Institute, International Academy at Santa Barbara; 1990–1996), GEOREF (Geo Reference Information System, American Geological Institute; 1990–1996), HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine; 1990–1996), Life Sciences (Cambridge Scientific Abstracts; 1990–1996), NTIS (National Technical Information Service, U.S. Department of Commerce; 1990–1996), Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1996), POLTOX (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1995), RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute for Occupational Safety and Health; 1996), Toxline (U.S. National Library of Medicine; 1990–1996), TRI93 (Toxic Chemical Release Inventory, U.S. Environmental Protection Agency, Office of Toxic Substances; 1993), USEPA-ASTER (Assessment Tools for the Evaluation of Risk, U.S. Environmental Protection Agency; up to December 21, 1994), WASTEINFO (Waste Management Information Bureau of the American Energy Agency; 1973 – September 1995), Water Resources Abstracts (U.S. Geological Survey, U.S. Department of the Interior; 1990–1996). A survey of Canadian industry was carried out under authority of Section 16 of CEPA (Environment Canada, 1997c). Companies were required to provide information on uses, releases, environmental concentrations, effects or other data that were available to them for ethylene oxide if they met the trigger quantity of 1000 kg ethylene oxide per year. Reveal Alert was used to maintain an ongoing record of the current scientific literature pertaining to the potential environmental effects of ethylene oxide. Data obtained after May 1998 were not considered in this assessment.

Health assessment

Data relevant to the assessment of the potential risks of ethylene oxide to human health were identified through evaluation of existing review documents of the U.S. Agency for Toxic Substances and Disease Registry (ATSDR, 1990), the International Programme on Chemical Safety (WHO, 1985) and the International Agency for Research on Cancer (IARC, 1994). To identify additional relevant toxicological data, literature searches on ethylene oxide were conducted using the strategy of searching by its name or CAS registry number, in the following databases: CCRIS (Chemical Carcinogenesis Research Information System, U.S. National Cancer Institute), Dialog, EMIC (Environmental Mutagen Information Center database, Oak Ridge National Laboratory) and EMICBACK (backfile of EMIC), ETICBACK (backfile of ETIC, Environmental Teratology Information Center database, U.S. Environmental Protection Agency and U.S. National Institute of Environmental Health Sciences), GENETOX (Genetic Toxicology, Office of Toxic Substances, U.S. Environmental Protection Agency), HSDB, IRIS (Integrated Risk Information System, U.S. Environmental Protection Agency) and RTECS. Ethylene oxide's name, registry number and major synonyms were searched in the ToxlinePlus (1985–1999) and Toxline (before 1985) databases. Its CAS registry number was searched in the Toxlit (1981–1999) database. The EMBASE database, for 1981–1999, was searched using the name, registry number and major synonyms, combined with a link to toxicological information. In addition to the above sources of information, numerous provincial and federal government officials and representatives of various industrial sectors were contacted between February and August of 1996 for data relevant to exposure and/or effects. Data relevant to human health obtained after January 1999 were not considered in this assessment.